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(54) Title: SMALL MOLECULE INHIBITORS OF TOLL-LIKE RECEPTOR 9

(57) Abstract: Small molecule compounds and compositions containing said compounds useful for inhibiting signaling by certain Toll-like receptors (TLRs), particularly TLR9, are provided. The compounds and compositions can be used to inhibit immune responses, including unwanted immune responses in particular. Compounds, compositions, and methods are provided to treat a variety of conditions involving unwanted immune responses, including for example autoimmune disease, inflammation, transplant rejection, and sepsis.

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SMALL MOLECULE INHIBITORS OF TOLL-LIKE RECEPTOR 9

FIELD OF THE INVENTION

The present invention relates generally to immunology. More particularly, the invention relates to small molecules capable of inhibiting an immune response, pharmaceutical compositions comprising the small molecule inhibitors, and methods of using the inhibitors.

BACKGROUND OF THE INVENTION

Stimulation of the immune system, which includes stimulation of either or both innate immunity and adaptive immunity, is a complex phenomenon that can result in either protective or adverse physiologic outcomes for the host. In recent years there has been increased interest in the mechanisms underlying innate immunity, which is believed to initiate and support adaptive immunity. This interest has been fueled in part by the recent discovery of a family of highly conserved pattern recognition receptor proteins known as Toll-like receptors (TLRs) believed to be involved in innate immunity as receptors for pathogen-associated molecular patterns (PAMPs). Compositions and methods useful for modulating innate immunity are therefore of great interest, as they may affect therapeutic approaches to conditions involving autoimmunity, inflammation, allergy, asthma, graft rejection, graft versus host disease (GvHD), infection, cancer, and immunodeficiency.

Recently there have been a number of reports describing the immunostimulatory effect of certain types of nucleic acid molecules, including CpG nucleic acids and double-stranded RNA. Of note, it was recently reported that Toll-like receptor 9 (TLR9) recognizes bacterial DNA and CpG DNA. Hemmi H et al. (2000) *Nature* 408:740-5; Bauer S et al. (2001) *Proc Natl Acad Sci U S A* 98:9237-42. It was also recently reported that immune complexes containing IgG and nucleic acid can stimulate TLR9 and participate in B-cell activation in certain autoimmune diseases. Leadbetter EA et al. (2002) *Nature* 416:595-8.

Chlroroquines have been recognized as useful not only as anti-malarial agents but also as anti-inflammatory agents. Although its mechanism of action is not well

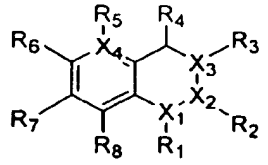
understood, chloroquine has been used effectively in the treatment of various autoimmune diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). For a review, see Wallace DJ (1996) *Lupus* 5 Suppl 1:S59-64. Recently Macfarlane and colleagues described a number of small molecule analogs and derivatives of chloroquine (4-aminoquinoline) and quinacrine (9-aminoacridine) which reportedly inhibit stimulation of the immune system. U.S. Pat. No. 6,221,882; U.S. Pat. No. 6,479,504; U.S. Pat. No. 6,521,637; published international patent application WO 00/76982; and published international patent application WO 99/01154. Macfarlane and colleagues report these small molecule inhibitors of the immune response, even when used at nanomolar concentrations, can block the action of immunostimulatory DNA. U.S. Pat. No. 6,221,882 B1. Macfarlane and coworkers studied a large number of compounds by varying substituents on a limited number of 4-aminoquinoline and 9-aminoacridine core structures related to chloroquine and quinacrine.

More recently Lipford et al. described yet additional small molecule TLR antagonists, including certain substituted quinoline and quinazoline compounds, in published patent application US 2005/0119273 A1.

SUMMARY OF THE INVENTION

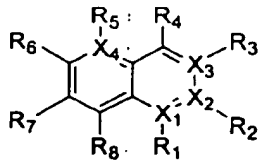
The present invention relates to compositions and methods useful for inhibiting an immune response.

The invention in one aspect is a compound having a structure



(I)

or



(II)

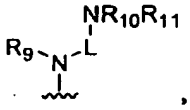
wherein

X_1, X_2, X_3, and X_4 are independently nitrogen or carbon;

R_1 and R_2 are independently absent, hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide;

R_3 is absent, hydrogen, optionally substituted alkyl, optionally substituted alkoxy, halide, Y_1, or Y_3;

R_4 is a group having the structure,



where R_9 is hydrogen or optionally substituted alkyl; L is optionally substituted alkyl; R_{10} and R_{11} are independently hydrogen or optionally substituted alkyl; and together R_{10} and R_{11} can be joined to form an optionally substituted heterocycle, or together R_9 and one of R_{10} or R_{11} can be joined to form an optionally substituted heterocycle;

R_5 is absent or hydrogen;

R_6 and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, halide, Y_1, or Y_2; and

R_8 is hydrogen, optionally substituted alkyl, optionally substituted alkoxy, halide, Y_1, or Y_3;

wherein

Y_1 is Ar-Y_2, where Ar is optionally substituted phenyl;

Y_2 is W-$L_1NR_{12}R_{13}$, where W is O, S, or NR_{14}; L_1 is optionally substituted alkyl; R_{12}, R_{13}, and R_{14} are independently hydrogen or optionally substituted alkyl; and together R_{12} and R_{13} can be joined to form an optionally substituted heterocycle, or together R_{14} and one of R_{12} or R_{13} can be joined to form an optionally substituted heterocycle;

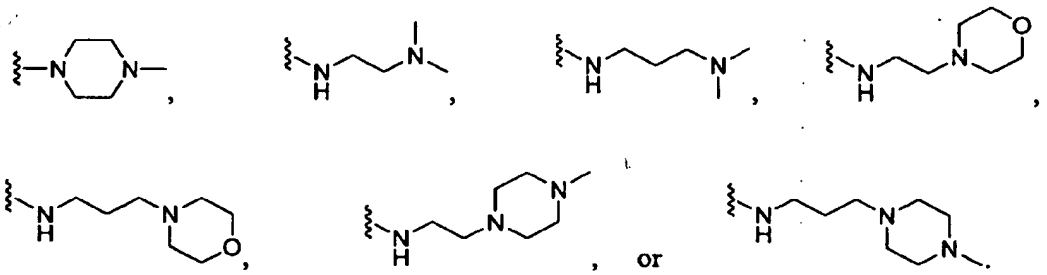
Y_3 is optionally substituted phenyl; and

at least one of R_3, R_6, R_7, and R_8 is Y_1; or at least one of R_6 and R_7 is Y_2; and/or at least one of R_3 and R_8 is Y_3.

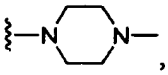
In one embodiment according to this aspect of the invention at least one of X_1, X_2, X_3, and X_4 is nitrogen.

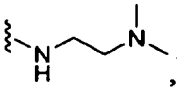
In one embodiment according to this aspect of the invention at least two of X_1, X_2, X_3, and X_4 are nitrogen.

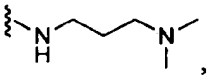
In one embodiment according to this and other aspects of the invention, R_4 is

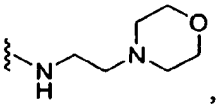


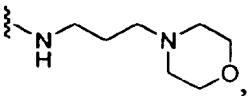
These groups are also referred to herein as follows:

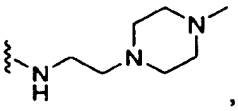
 , 1-(4-methyl-piperazine) or, equivalently, pip;

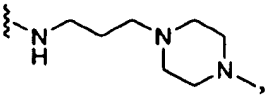
 , N-[N,N-dimethylethylenediamine] or, equivalently, diamine;

 , N-[N,N-dimethylpropane-1,3-diamine] or, equivalently, dipamine;

 , (2-morpholin-4-yl-ethyl)-amine or, equivalently, dimor;

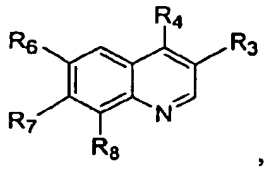
 , (3-morpholin-4-yl-propyl)-amine or, equivalently, dipmor;

 , [3-(4-methylpiperazin-1-yl-ethyl)]-amine or, equivalently, dipip; and

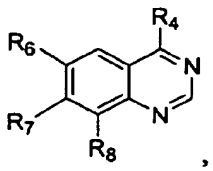
 , [3-(4-methylpiperazin-1-yl-propyl)]-amine or, equivalently, dippip.

In one embodiment according to this aspect of the invention Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip.

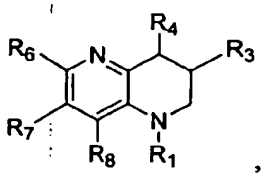
In one embodiment the compound has one of the following structures,



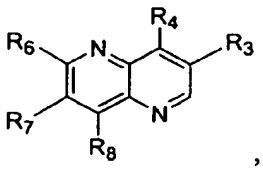
(III)



(IV)

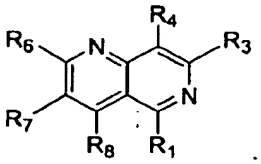


(V)



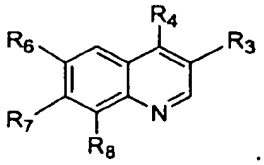
(VI)

or



(VII)

In one embodiment the compound has the structure



(III)

Further according to this embodiment, in one embodiment R_6 is Y_1.

Further still according to this embodiment in which R_6 is Y_1, in one embodiment R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_6 is Y_1, in one embodiment R_3, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_1 and R_3, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_1, R_3, R_7, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2 is specifically embraced by the latter embodiment, i.e.,

R_4 pip and Y_2 pip; R_4 pip and Y_2 diamine; R_4 pip and Y_2 dipamine; R_4 pip and Y_2 dimor; R_4 pip and Y_2 dipmor; R_4 pip and Y_2 dipip; R_4 pip and Y_2 dippip;

R_4 diamine and Y_2 pip; R_4 diamine and Y_2 diamine; R_4 diamine and Y_2 dipamine; R_4 diamine and Y_2 dimor; R_4 diamine and Y_2 dipmor; R_4 diamine and Y_2 dipip; R_4 diamine and Y_2 dippip;

R_4 dipamine and Y_2 pip; R_4 dipamine and Y_2 diamine; R_4 dipamine and Y_2 dipamine; R_4 dipamine and Y_2 dimor; R_4 dipamine and Y_2 dipmor; R_4 dipamine and Y_2 dipip; R_4 dipamine and Y_2 dippip;

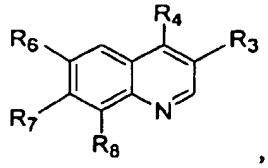
R_4 dimor and Y_2 pip; R_4 dimor and Y_2 diamine; R_4 dimor and Y_2 dipamine; R_4 dimor and Y_2 dimor; R_4 dimor and Y_2 dipmor; R_4 dimor and Y_2 dipip; R_4 dimor and Y_2 dippip;

R_4 dipmor and Y_2 pip; R_4 dipmor and Y_2 diamine; R_4 dipmor and Y_2 dipamine; R_4 dipmor and Y_2 dimor; R_4 dipmor and Y_2 dipmor; R_4 dipmor and Y_2 dipip; R_4 dipmor and Y_2 dippip;

R_4 dipip and Y_2 pip; R_4 dipip and Y_2 diamine; R_4 dipip and Y_2 dipamine; R_4 dipip and Y_2 dimor; R_4 dipip and Y_2 dipmor; R_4 dipip and Y_2 dipip; R_4 dipip and Y_2 dippip;

R_4 dippip and Y_2 pip; R_4 dippip and Y_2 diamine; R_4 dippip and Y_2 dipamine; R_4 dippip and Y_2 dimor; R_4 dippip and Y_2 dipmor; R_4 dippip and Y_2 dipip; R_4 dippip and Y_2 dippip.

In one embodiment the compound has the structure



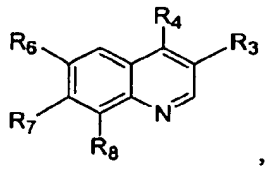
(III)

wherein R_7 is Y_1.

Further according to this embodiment in which R_7 is Y_1, in one embodiment R_3, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_7 is Y_1, in one embodiment R_3, R_6, and R_8 are hydrogen. Further still according to this embodiment in which R_7 is Y_1 and R_3, R_6, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according

to this embodiment in which R_7 is Y_1, R_3, R_6, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

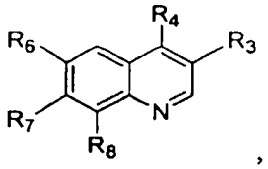


(III)

wherein R_8 is Y_1.

Further according to this embodiment in which R_8 is Y_1, in one embodiment R_3, R_6, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_8 is Y_1, in one embodiment R_3, R_6, and R_7 are hydrogen. Further still according to this embodiment in which R_8 is Y_1 and R_3, R_6, and R_7 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_8 is Y_1, R_3, R_6, and R_7 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure



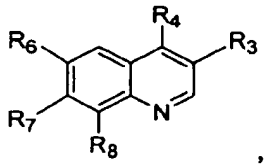
(III)

wherein R_3 is Y_1.

Further according to this embodiment in which R_3 is Y_1, in one embodiment R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_3 is Y_1, in one embodiment R_6, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_3 is Y_1 and R_6, R_7, and R_8 are hydrogen, in one embodiment

R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_3 is Y_1, and R_3, R_6, and R_7 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

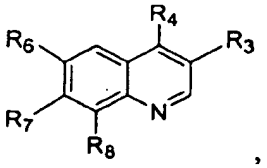


(III)

wherein R_6 is Y_2 and R_8 is Y_3.

Further according to this embodiment in which R_6 is Y_2 and R_8 is Y_3, in one embodiment R_3 and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_6 is Y_2 and R_8 is Y_3, in one embodiment R_3 and R_7 are hydrogen. Further still according to this embodiment in which R_6 is Y_2, R_8 is Y_3, and R_3 and R_7 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_2, R_8 is Y_3, R_3 and R_7 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure



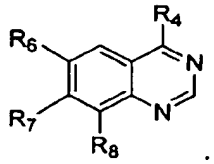
(III)

wherein R_3 is Y_3 and R_7 is Y_2.

Further according to this embodiment in which R_3 is Y_3 and R_7 is Y_2, in one embodiment R_6 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in

which R_3 is Y_3 and R_7 is Y_2, in one embodiment R_6 and R_8 are hydrogen. Further still according to this embodiment in which R_3 is Y_3, R_7 is Y_2, and R_6 and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_3 is Y_3, R_7 is Y_2, R_6 and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

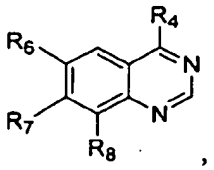


(IV)

Further according to this embodiment, in one embodiment R_6 is Y_1.

Further still according to this embodiment in which R_6 is Y_1, in one embodiment R_7 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_6 is Y_1, in one embodiment R_7 and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_1 and R_7 and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_1, R_7 and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

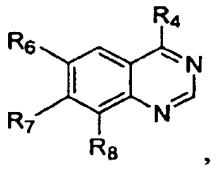


(IV)

wherein R_7 is Y_1.

Further still according to this embodiment in which R_7 is Y_1, in one embodiment R_6 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_7 is Y_1, in one embodiment R_6 and R_8 are hydrogen. Further still according to this embodiment in which R_7 is Y_1 and R_6 and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_7 is Y_1, R_6 and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

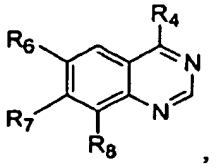


(IV)

wherein R_8 is Y_1.

Further still according to this embodiment in which R_8 is Y_1, in one embodiment R_6 and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_8 is Y_1, in one embodiment R_6 and R_7 are hydrogen. Further still according to this embodiment in which R_8 is Y_1 and R_6 and R_7 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_8 is Y_1, R_6 and R_7 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

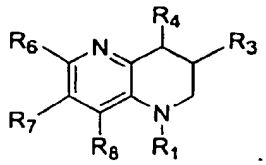


(IV)

wherein R_6 is Y_2 and R_8 is Y_3.

Further still according to this embodiment in which R_6 is Y_2 and R_8 is Y_3, in one embodiment R_7 is hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_6 is Y_2 and R_8 is Y_3, in one embodiment R_7 is hydrogen. Further still according to this embodiment in which R_6 is Y_2, R_8 is Y_3, and R_7 is hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_2, R_8 is Y_3, R_7 is hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

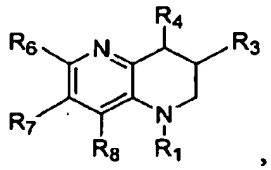


(V)

Further according to this embodiment, in one embodiment R_1 is hydrogen and R_6 is Y_1.

Further still according to this embodiment in which R_1 is hydrogen and R_6 is Y_1, in one embodiment R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_1 is hydrogen and R_6 is Y_1, in one embodiment R_3, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_1 is hydrogen, R_6 is Y_1, and R_3, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_1 is hydrogen and R_6 is Y_1, R_3, R_7, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

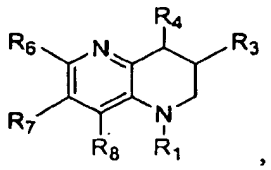


(V)

wherein R_1 is hydrogen and R_7 is Y_1.

Further still according to this embodiment in which R_1 is hydrogen and R_7 is Y_1, in one embodiment R_3, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_1 is hydrogen and R_7 is Y_1, in one embodiment R_3, R_6, and R_8 are hydrogen. Further still according to this embodiment in which R_1 is hydrogen, R_7 is Y_1, and R_3, R_6, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_1 is hydrogen and R_7 is Y_1, R_3, R_6, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure



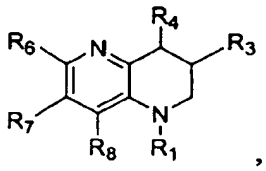
(V)

wherein R_1 is hydrogen and R_8 is Y_1.

Further still according to this embodiment in which R_1 is hydrogen and R_8 is Y_1, in one embodiment R_3, R_6, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_1 is hydrogen and R_8 is Y_1, in one embodiment R_3, R_6, and R_7 are hydrogen. Further still according to this embodiment in which R_1 is hydrogen, R_8 is Y_1, and R_3, R_6, and R_7 are hydrogen, in one embodiment R_4 is pip,

diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_1 is hydrogen and R_8 is Y_1, R_3, R_6, and R_7 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

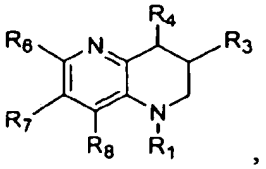


(V)

wherein R_1 is hydrogen and R_3 is Y_1.

Further still according to this embodiment in which R_1 is hydrogen and R_3 is Y_1, in one embodiment R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_1 is hydrogen and R_3 is Y_1, in one embodiment R_6, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_1 is hydrogen, R_3 is Y_1, and R_6, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_1 is hydrogen and R_3 is Y_1, R_6, R_7, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

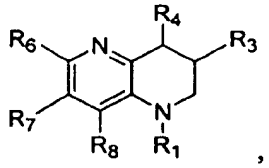


(V)

wherein R_1 is hydrogen, R_6 is Y_2, and R_8 is Y_3.

Further still according to this embodiment in which R_1 is hydrogen, R_6 is Y_2, and R_8 is Y_3, in one embodiment R_3 and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_1 is hydrogen, R_6 is Y_2, and R_8 is Y_3, in one embodiment R_3 and R_7 are hydrogen. Further still according to this embodiment in which R_1 is hydrogen, R_6 is Y_2, R_8 is Y_3, and R_3 and R_7 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_1 is hydrogen, R_6 is Y_2, R_8 is Y_3, R_3 and R_7 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

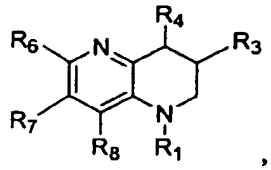


(V)

wherein R_1 is hydrogen, R_3 is Y_3, and R_7 is Y_2.

Further still according to this embodiment in which R_1 is hydrogen, R_3 is Y_3, and R_7 is Y_2, in one embodiment R_6 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_1 is hydrogen, R_3 is Y_3, and R_7 is Y_2, in one embodiment R_6 and R_8 are hydrogen. Further still according to this embodiment in which R_1 is hydrogen, R_3 is Y_3, R_7 is Y_2, and R_6 and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_1 is hydrogen, R_3 is Y_3, R_7 is Y_2, R_6 and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

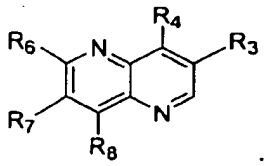


(V)

wherein R_1 is Y_3 and R_7 is Y_2.

Further still according to this embodiment in which R_1 is Y_3 and R_7 is Y_2, in one embodiment R_3, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_1 is Y_3 and R_7 is Y_2, in one embodiment R_3, R_6, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_1 is Y_3, R_7 is Y_2, and R_3, R_6, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_1 is Y_3 and R_7 is Y_2, R_3, R_6, R_7, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure



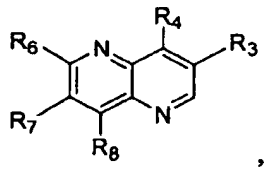
(VI)

Further according to this embodiment, in one embodiment R_6 is Y_1.

Further still according to this embodiment in which R_6 is Y_1, in one embodiment R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_6 is Y_1, in one embodiment R_3, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_1 and R_3, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_1, R_3, R_7, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and

every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

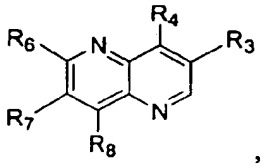


(VI)

wherein R_7 is Y_1.

Further still according to this embodiment in which R_7 is Y_1, in one embodiment R_3, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_7 is Y_1, in one embodiment R_3, R_6, and R_8 are hydrogen. Further still according to this embodiment in which R_7 is Y_1, and R_3, R_6, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_7 is Y_1, R_3, R_6, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure



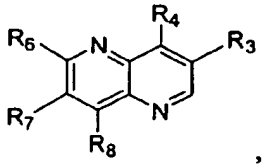
(VI)

wherein R_8 is Y_1.

Further still according to this embodiment in which R_8 is Y_1, in one embodiment R_3, R_6, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_8 is Y_1, in one embodiment R_3, R_6, and R_7 are hydrogen. Further still according to this embodiment in which R_8 is Y_1, and R_3, R_6, and R_7 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip.

Further still according to this embodiment in which R_8 is Y_1, R_3, R_6, and R_7 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

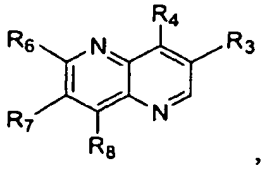


(VI)

wherein R_3 is Y_1.

Further still according to this embodiment in which R_3 is Y_1, in one embodiment R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_3 is Y_1, in one embodiment R_6, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_3 is Y_1, and R_6, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_3 is Y_1, R_6, R_7, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure



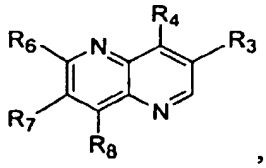
(VI)

wherein R_6 is Y_2 and R_8 is Y_3.

Further still according to this embodiment in which R_6 is Y_2 and R_8 is Y_3, in one embodiment R_3 and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in

which R_6 is Y_2 and R_8 is Y_3, in one embodiment R_3 and R_7 are hydrogen. Further still according to this embodiment in which R_6 is Y_2, R_8 is Y_3, and R_3 and R_7 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_2 and R_8 is Y_3, R_3 and R_7 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

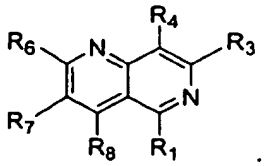


(VI)

wherein R_3 is Y_3 and R_7 is Y_2.

Further still according to this embodiment in which R_3 is Y_3 and R_7 is Y_2, in one embodiment R_6 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_3 is Y_3 and R_7 is Y_2, in one embodiment R_6 and R_8 are hydrogen. Further still according to this embodiment in which R_3 is Y_3, R_7 is Y_2, and R_6 and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_3 is Y_3 and R_7 is Y_2, R_6 and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

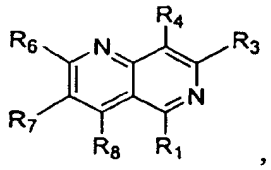


(VII)

Further according to this embodiment, in one embodiment R_6 is Y_1.

Further still according to this embodiment in which R_6 is Y_1, in one embodiment R_1, R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_6 is Y_1, in one embodiment R_1, R_3, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_1 and R_1, R_3, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_1, R_1, R_3, R_7, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

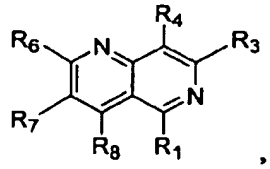


(VII)

wherein R_7 is Y_1.

Further still according to this embodiment in which R_7 is Y_1, in one embodiment R_1, R_3, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_7 is Y_1, in one embodiment R_1, R_3, R_6, and R_8 are hydrogen. Further still according to this embodiment in which R_7 is Y_1 and R_1, R_3, R_6, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_7 is Y_1, R_1, R_3, R_6, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

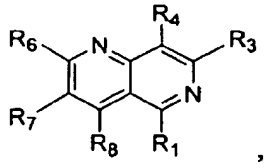


(VII)

wherein R_8 is Y_1.

Further still according to this embodiment in which R_8 is Y_1, in one embodiment R_1, R_3, R_6, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_8 is Y_1, in one embodiment R_1, R_3, R_6, and R_7 are hydrogen. Further still according to this embodiment in which R_8 is Y_1 and R_1, R_3, R_6, and R_7 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_8 is Y_1, R_1, R_3, R_6, and R_7 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure



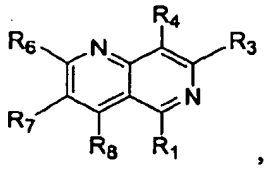
(VII)

wherein R_3 is Y_1.

Further still according to this embodiment in which R_3 is Y_1, in one embodiment R_1, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_3 is Y_1, in one embodiment R_1, R_6, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_3 is Y_1 and R_1, R_6, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_3 is Y_1, R_1, R_6, R_7, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or

dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

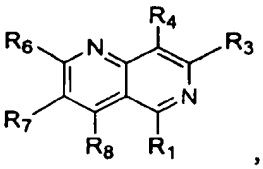


(VII)

wherein R_6 is Y_2 and R_8 is Y_3.

Further still according to this embodiment in which R_6 is Y_2 and R_8 is Y_3, in one embodiment R_1, R_3, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_6 is Y_2 and R_8 is Y_3, in one embodiment R_1, R_3, and R_7 are hydrogen. Further still according to this embodiment in which R_6 is Y_2, R_8 is Y_3, and R_1, R_3, and R_7 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_2 and R_8 is Y_3, R_1, R_3, and R_7 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure



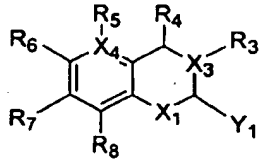
(VII)

wherein R_3 is Y_3 and R_7 is Y_2.

Further still according to this embodiment in which R_3 is Y_3 and R_7 is Y_2, in one embodiment R_1, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further still according to this embodiment in which R_3 is Y_3 and R_7 is Y_2, in one embodiment R_1, R_6, and R_8 are hydrogen. Further still according to this embodiment in which R_3 is Y_3, R_7 is Y_2, and R_1, R_6, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor,

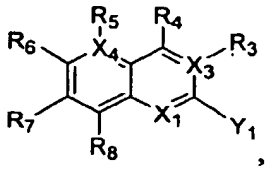
dipmor, dipip, or dippip. Further still according to this embodiment in which R_3 is Y_3 and R_7 is Y_2, R_1, R_6, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

The invention in one aspect is a compound having a structure



(VIII)

or



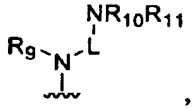
(IX),

wherein

X_1, X_3, and X_4 are independently nitrogen or carbon;

R_3 is absent, hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide;

R_4 is a group having the structure,



where R_9 is hydrogen or optionally substituted alkyl; L is optionally substituted alkyl; R_{10} and R_{11} are independently hydrogen or optionally substituted alkyl; and together R_{10} and R_{11} can be joined to form an optionally substituted heterocycle, or together R_9 and one of R_{10} or R_{11} can be joined to form an optionally substituted heterocycle;

R_5 is absent, hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide;

R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide; and

Y_1 is Ar-Y_2, where Ar is optionally substituted phenyl;

wherein

Y_2 is W-$L_1NR_{12}R_{13}$, where W is O, S, or NR_{14}; L_1 is optionally substituted alkyl; R_{12}, R_{13}, and R_{14} are independently hydrogen or optionally substituted alkyl; and together R_{12} and R_{13} can be joined to form an optionally substituted heterocycle,

or together R_{14} and one of R_{12} or R_{13} can be joined to form an optionally substituted heterocycle;

wherein, when the compound has the structure (IX) wherein X_3 is nitrogen, X_4 is nitrogen.

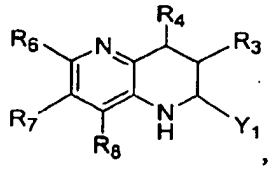
In one embodiment according to this aspect of the invention at least one of X_1, X_3, and X_4 is nitrogen.

In one embodiment according to this aspect of the invention at least two of X_1, X_3, and X_4 are nitrogen.

In one embodiment according to this aspect of the invention, R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, as disclosed above.

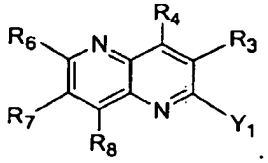
In one embodiment according to this aspect of the invention Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip.

In one embodiment the compound has the structure



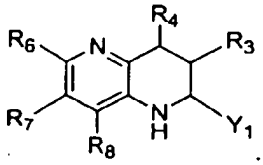
(X)

or



(XI)

In one embodiment the compound has the structure

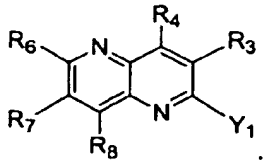


(X)

Further according to this embodiment, in one embodiment R_3, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment, in one embodiment R_3, R_6, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_3, R_6, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_3, R_6, R_7, and R_8 are hydrogen and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or

dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

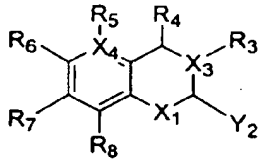
In one embodiment the compound has the structure



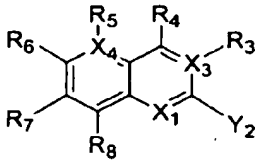
(XI)

Further according to this embodiment, in one embodiment R_3, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment, in one embodiment R_3, R_6, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_3, R_6, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_3, R_6, R_7, and R_8 are hydrogen and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

The invention in one aspect is a compound having a structure



or



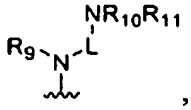
(XII) (XIII)

wherein

X_1, X_3, and X_4 are independently nitrogen or carbon;

R_3 is absent, hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide;

R_4 is a group having the structure,



where R_9 is hydrogen or optionally substituted alkyl; L is optionally substituted alkyl; R_{10} and R_{11} are independently hydrogen or optionally substituted

alkyl; and together R_{10} and R_{11} can be joined to form an optionally substituted heterocycle, or together R_9 and one of R_{10} or R_{11} can be joined to form an optionally substituted heterocycle;

R_5 is absent or hydrogen;

R_6 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, halide, or Y_3;

R_7 is hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide; and

Y_2 is $W\text{-}L_1NR_{12}R_{13}$, where W is O, S, or NR_{14}; L_1 is optionally substituted alkyl; R_{12}, R_{13}, and R_{14} are independently hydrogen or optionally substituted alkyl; and together R_{12} and R_{13} can be joined to form an optionally substituted heterocycle, or together R_{14} and one of R_{12} or R_{13} can be joined to form an optionally substituted heterocycle;

wherein

Y_3 is optionally substituted phenyl.

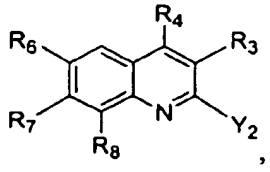
In one embodiment according to this aspect of the invention at least one of X_1, X_3, and X_4 is nitrogen.

In one embodiment according to this aspect of the invention at least two of X_1, X_3, and X_4 are nitrogen.

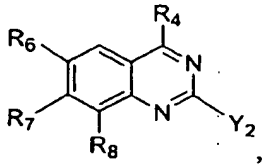
In one embodiment according to this aspect of the invention, R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, as disclosed above.

In one embodiment according to this aspect of the invention Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip.

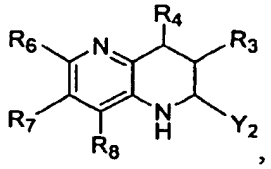
In one embodiment the compound has the structure



(XIV)

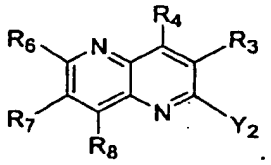


(XV)



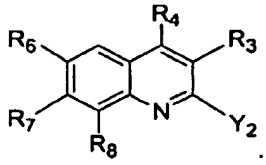
(XVI)

or



(XVII)

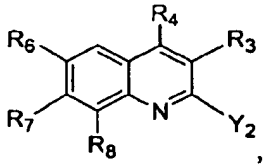
In one embodiment the compound has the structure



(XIV)

Further according to this embodiment, in one embodiment R_6 is Y_3. Further according to this embodiment in which R_6 is Y_3, in one embodiment R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_6 is Y_3, in one embodiment R_3, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_3 and R_3, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_3, R_3, R_7, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

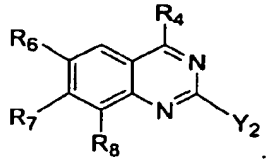


(XIV)

wherein R_8 is Y_3. Further according to this embodiment in which R_8 is Y_3, in one embodiment R_3, R_6, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_8 is Y_3, in one embodiment R_3, R_6, and R_7 are hydrogen. Further still according to this embodiment in which R_8 is Y_3 and R_3, R_6, and R_7 are hydrogen, in

one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_8 is Y_3, R_3, R_6, and R_7 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

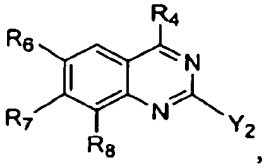
In one embodiment the compound has the structure



(XV)

Further according to this embodiment, in one embodiment R_6 is Y_3. Further according to this embodiment in which R_6 is Y_3, in one embodiment R_7 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_6 is Y_3, in one embodiment R_7 and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_3 and R_7 and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_3, R_7 and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

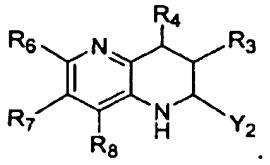


(XV)

wherein R_8 is Y_3. Further according to this embodiment in which R_8 is Y_3, in one embodiment R_6 and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_8 is Y_3, in one embodiment R_6 and R_7 are hydrogen. Further still according to

this embodiment in which R_8 is Y_3 and R_6 and R_7 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_8 is Y_3, R_6 and R_7 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

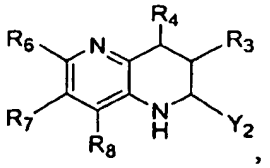
In one embodiment the compound has the structure



(XVI)

Further according to this embodiment, in one embodiment R_6 is Y_3. Further according to this embodiment in which R_6 is Y_3, in one embodiment R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_6 is Y_3, in one embodiment R_3, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_3 and R_3, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_3, R_3, R_7, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

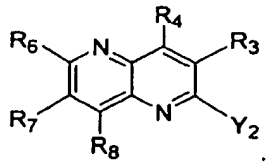


(XVI)

wherein R_8 is Y_3. Further according to this embodiment in which R_8 is Y_3, in one embodiment R_3, R_6, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_8 is Y_3, in one embodiment R_3, R_6, and R_7 are hydrogen. Further still

according to this embodiment in which R_8 is Y_3 and R_3, R_6, and R_7 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_8 is Y_3, R_3, R_6, and R_7 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

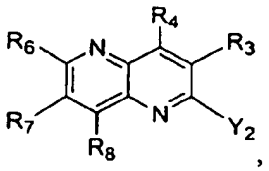
In one embodiment the compound has the structure



(XVII)

Further according to this embodiment, in one embodiment R_6 is Y_3. Further according to this embodiment in which R_6 is Y_3, in one embodiment R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_6 is Y_3, in one embodiment R_3, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_3 and R_3, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_3, R_3, R_7, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

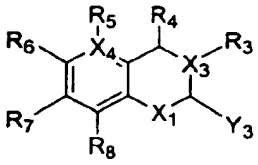


(XVII)

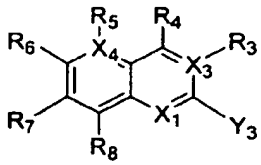
wherein R_8 is Y_3. Further according to this embodiment in which R_8 is Y_3, in one embodiment R_3, R_6, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in

which R_8 is Y_3, in one embodiment R_3, R_6, and R_7 are hydrogen. Further still according to this embodiment in which R_8 is Y_3 and R_3, R_6, and R_7 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_8 is Y_3, R_3, R_6, and R_7 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

The invention in one aspect is a compound having a structure



or



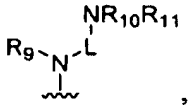
(XVIII) (XIX)

wherein

X_1, X_3, and X_4 are independently nitrogen or carbon;

R_3 is absent, hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide;

R_4 is a group having the structure,



where R_9 is hydrogen or optionally substituted alkyl; L is optionally substituted alkyl; R_{10} and R_{11} are independently hydrogen or optionally substituted alkyl; and together R_{10} and R_{11} can be joined to form an optionally substituted heterocycle, or together R_9 and one of R_{10} or R_{11} can be joined to form an optionally substituted heterocycle;

R_5 is absent or hydrogen;

R_6 and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, halide, or Y_2;

R_8 is hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide; and

Y_3 is optionally substituted phenyl;

wherein

Y_2 is W-$L_1NR_{12}R_{13}$, where W is O, S, or NR_{14}; L_1 is optionally substituted alkyl; R_{12}, R_{13}, and R_{14} are independently hydrogen or optionally substituted alkyl; and together R_{12} and R_{13} can be joined to form an optionally substituted heterocycle, or together R_{14} and one of R_{12} or R_{13} can be joined to form an optionally substituted heterocycle.

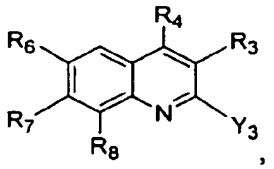
In one embodiment according to this aspect of the invention at least one of X_1, X_3, and X_4 is nitrogen.

In one embodiment according to this aspect of the invention at least two of X_1, X_3, and X_4 are nitrogen.

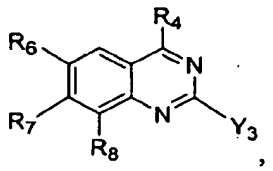
In one embodiment according to this aspect of the invention, R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, as disclosed above.

In one embodiment according to this aspect of the invention Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip.

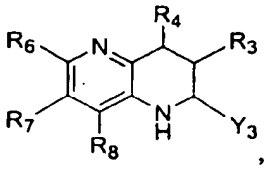
In one embodiment the compound has the structure



(XX)

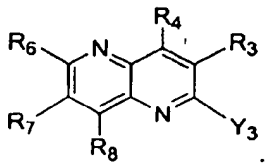


(XXI)



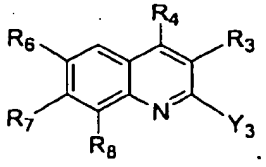
(XXII)

or



(XXIII)

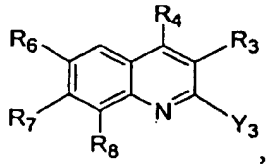
In one embodiment the compound has the structure



(XX)

Further according to this embodiment, in one embodiment R_6 is Y_2. Further according to this embodiment in which R_6 is Y_2, in one embodiment R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_6 is Y_2, in one embodiment R_3, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_2 and R_3, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_2, R_3, R_7, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

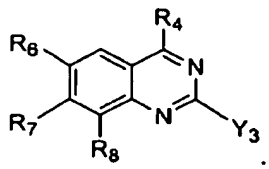
In one embodiment the compound has the structure



(XX)

wherein R_7 is Y_2. Further according to this embodiment in which R_7 is Y_2, in one embodiment R_3, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_7 is Y_2, in one embodiment R_3, R_6, and R_8 are hydrogen. Further still according to this embodiment in which R_7 is Y_2 and R_3, R_6, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_7 is Y_2, R_3, R_6, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

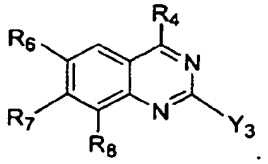
In one embodiment the compound has the structure



(XXI)

Further according to this embodiment, in one embodiment R_6 is Y_2. Further according to this embodiment in which R_6 is Y_2, in one embodiment R_7 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_6 is Y_2, in one embodiment R_7 and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_2 and R_7 and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_2, R_7 and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

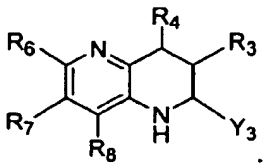
In one embodiment the compound has the structure



(XXI)

wherein R_7 is Y_2. Further according to this embodiment in which R_7 is Y_2, in one embodiment R_6 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_7 is Y_2, in one embodiment R_6 and R_8 are hydrogen. Further still according to this embodiment in which R_7 is Y_2 and R_6 and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_7 is Y_2, R_6 and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

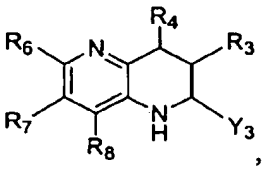
In one embodiment the compound has the structure



(XXII)

Further according to this embodiment, in one embodiment R_6 is Y_2. Further according to this embodiment in which R_6 is Y_2, in one embodiment R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_6 is Y_2, in one embodiment R_3, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_2 and R_3, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_2, R_3, R_7, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

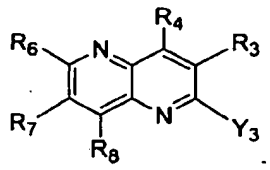
In one embodiment the compound has the structure



(XXII)

wherein R_7 is Y_2. Further according to this embodiment in which R_7 is Y_2, in one embodiment R_3, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_7 is Y_2, in one embodiment R_3, R_6, and R_8 are hydrogen. Further still according to this embodiment in which R_7 is Y_2 and R_3, R_6, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_7 is Y_2, R_3, R_6, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

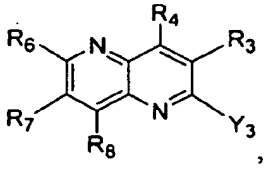
In one embodiment the compound has the structure



(XXIII)

Further according to this embodiment, in one embodiment R_6 is Y_2. Further according to this embodiment in which R_6 is Y_2, in one embodiment R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_6 is Y_2, in one embodiment R_3, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_2 and R_3, R_7, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_2, R_3, R_7, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

In one embodiment the compound has the structure

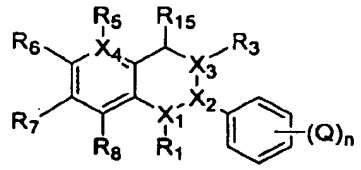


(XXIII)

wherein R_7 is Y_2. Further according to this embodiment in which R_7 is Y_2, in one embodiment R_3, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which R_7 is Y_2, in one embodiment R_3, R_6, and R_8 are hydrogen. Further still according to this embodiment in which R_7 is Y_2 and R_3, R_6, and R_8 are hydrogen, in one embodiment R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_7 is Y_2, R_3, R_6, and R_8 are hydrogen, and R_4 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, in one embodiment Y_2 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and

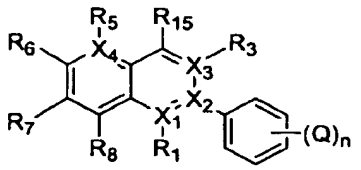
every combination of R_4 and Y_2, as set forth above, is specifically embraced by the latter embodiment.

The invention in one aspect is a compound having a structure



(XXIV)

or



(XXV)

wherein

X_1, X_2, X_3, and X_4 are independently nitrogen or carbon;

R_1, R_3, and R_5 are independently absent, hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide;

R_6 is independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, halide, or Y_2;

R_7, R_8, and R_{15} are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide;

each Q is independently optionally substituted alkyl or Y_2; and

n is an integer from 1-5;

wherein

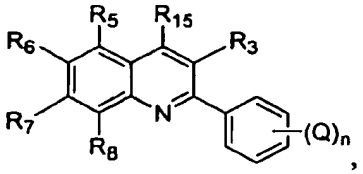
Y_2 is W-$L_1NR_{12}R_{13}$, where W is O, S, or NR_{14}; L_1 is optionally substituted alkyl; R_{12}, R_{13}, and R_{14} are independently hydrogen or optionally substituted alkyl; and together R_{12} and R_{13} can be joined to form an optionally substituted heterocycle, or together R_{14} and one of R_{12} or R_{13} can be joined to form an optionally substituted heterocycle.

In one embodiment according to this aspect of the invention, at least one of X_1, X_2, X_3, and X_4 is nitrogen.

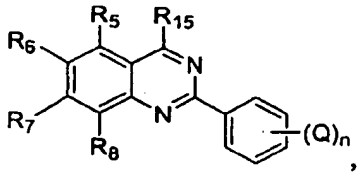
In one embodiment according to this aspect of the invention, at least two of X_1, X_2, X_3, and X_4 are nitrogen.

In one embodiment according to this aspect of the invention, at least one Q is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip, as disclosed above.

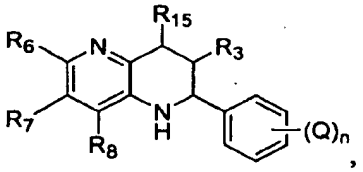
In one embodiment the compound has the structure



(XXVI)

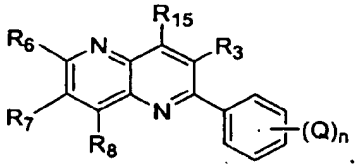


(XXVII)



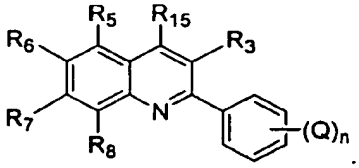
(XXVIII)

or



(XXIX)

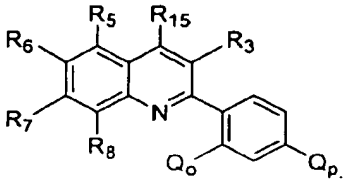
In one embodiment the compound has the structure



(XXVI)

Further according to this embodiment, in one embodiment each and every Q is Y_2.

In one embodiment the compound has the structure

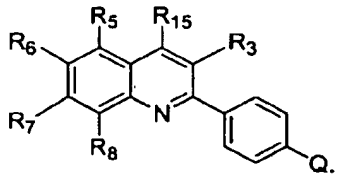


(XXX)

Further according to this embodiment, in one embodiment Q_p and Q_o are independently Y_2. Further according to this embodiment in which Q_p and Q_o are independently Y_2, in one embodiment R_3, R_{15}, R_5, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which Q_p and Q_o are independently Y_2, in one embodiment R_3, R_{15}, R_5, R_6, R_7, and R_8 are hydrogen. Further still according to this embodiment in which Q_p and Q_o are independently Y_2 and R_3, R_{15}, R_5, R_6, R_7, and R_8 are hydrogen, in one embodiment Q_p is pip, diamine, dipamine, dimor,

dipmor, dipip, or dippip. Further still according to this embodiment in which Q_p and Q_o are independently Y_2 and R_3, R_{15}, R_5, R_6, R_7, and R_8 are hydrogen, in one embodiment Q_o is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which Q_p and Q_o are independently Y_2 and R_3, R_{15}, R_5, R_6, R_7, and R_8 are hydrogen, in one embodiment Q_p and Q_o are independently pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of Q_p and Q_o, analogous to each and every combination of R_4 and Y_2 as set forth above, is specifically embraced by this this latter embodiment.

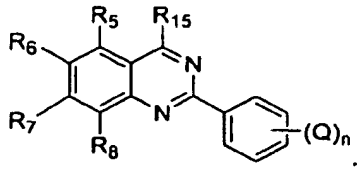
In one embodiment the compound has the structure



(XXXI)

Further according to this embodiment, in one embodiment R_6 is Y_2. Further according to this embodiment in which R_6 is Y_2, in one embodiment Q is independently Y_2. Further still according to this embodiment in which R_6 is Y_2 and Q is independently Y_2, in one embodiment R_3, R_{15}, R_5, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_2, Q is independently Y_2, and R_3, R_{15}, R_5, R_7, and R_8 are hydrogen, in one embodiment R_6 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_2, Q is independently Y_2, and R_3, R_{15}, R_5, R_7, and R_8 are hydrogen, in one embodiment R_6 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 and Q are independently Y_2, and R_3, R_{15}, R_5, R_6, R_7, and R_8 are hydrogen, in one embodiment R_6 and Q are independently pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_6 and Q, analogous to each and every combination of R_4 and Y_2 as set forth above, is specifically embraced by this latter embodiment.

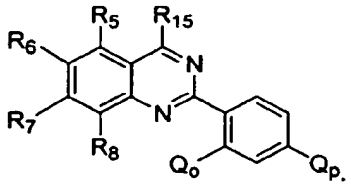
In one embodiment the compound has the structure



(XXVII)

Further according to this embodiment, in one embodiment each and every Q is Y_2.

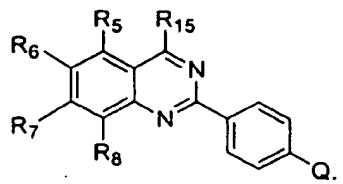
In one embodiment the compound has the structure



(XXXII)

Further according to this embodiment, in one embodiment Q_p and Q_o are independently Y_2. Further according to this embodiment in which Q_p and Q_o are independently Y_2, in one embodiment R_{15}, R_5, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which Q_p and Q_o are independently Y_2, in one embodiment R_{15}, R_5, R_6, R_7, and R_8 are hydrogen. Further still according to this embodiment in which Q_p and Q_o are independently Y_2 and R_{15}, R_5, R_6, R_7, and R_8 are hydrogen, in one embodiment Q_p is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which Q_p and Q_o are independently Y_2 and R_{15}, R_5, R_6, R_7, and R_8 are hydrogen, in one embodiment Q_o is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which Q_p and Q_o are independently Y_2 and R_{15}, R_5, R_6, R_7, and R_8 are hydrogen, in one embodiment Q_p and Q_o are independently pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of Q_p and Q_o, analogous to each and every combination of R_4 and Y_2 as set forth above, is specifically embraced by this this latter embodiment.

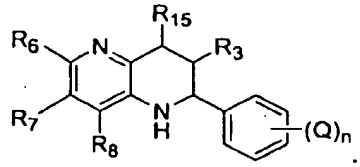
In one embodiment the compound has the structure



(XXXIII)

Further according to this embodiment, in one embodiment R_6 is Y_2. Further according to this embodiment in which R_6 is Y_2, in one embodiment Q is independently Y_2. Further still according to this embodiment in which R_6 is Y_2 and Q is independently Y_2, in one embodiment R_{15}, R_5, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_2, Q is independently Y_2, and R_{15}, R_5, R_7, and R_8 are hydrogen, in one embodiment R_6 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_2, Q is independently Y_2, and R_{15}, R_5, R_7, and R_8 are hydrogen, in one embodiment R_6 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 and Q are independently Y_2, and R_{15}, R_5, R_6, R_7, and R_8 are hydrogen, in one embodiment R_6 and Q are independently pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_6 and Q, analogous to each and every combination of R_4 and Y_2 as set forth above, is specifically embraced by this latter embodiment.

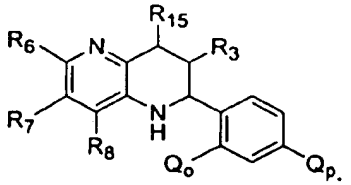
In one embodiment the compound has the structure



(XXVIII)

Further according to this embodiment, in one embodiment each and every Q is Y_2.

In one embodiment the compound has the structure

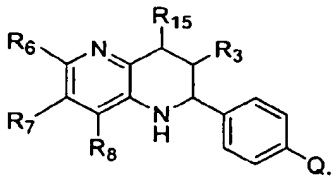


(XXXIV)

Further according to this embodiment, in one embodiment Q_p and Q_o are independently Y_2. Further according to this embodiment in which Q_p and Q_o are independently Y_2, in one embodiment R_3, R_{15}, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which Q_p and Q_o are independently Y_2, in

one embodiment R_3, R_{15}, R_6, R_7, and R_8 are hydrogen. Further still according to this embodiment in which Q_p and Q_o are independently Y_2 and R_3, R_{15}, R_6, R_7, and R_8 are hydrogen, in one embodiment Q_p is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which Q_p and Q_o are independently Y_2 and R_3, R_{15}, R_6, R_7, and R_8 are hydrogen, in one embodiment Q_o is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which Q_p and Q_o are independently Y_2 and R_{15}, R_5, R_6, R_7, and R_8 are hydrogen, in one embodiment Q_p and Q_o are independently pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of Q_p and Q_o, analogous to each and every combination of R_4 and Y_2 as set forth above, is specifically embraced by this this latter embodiment.

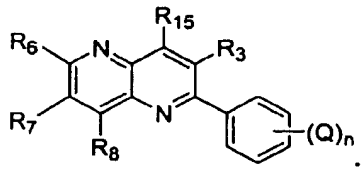
In one embodiment the compound has the structure



(XXXV)

Further according to this embodiment, in one embodiment R_6 is Y_2. Further according to this embodiment in which R_6 is Y_2, in one embodiment Q is independently Y_2. Further still according to this embodiment in which R_6 is Y_2 and Q is independently Y_2, in one embodiment R_3, R_{15}, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_2, Q is independently Y_2, and R_3, R_{15}, R_7, and R_8 are hydrogen, in one embodiment R_6 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_2, Q is independently Y_2, and R_3, R_{15}, R_7, and R_8 are hydrogen, in one embodiment R_6 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 and Q are independently Y_2, and R_3, R_{15}, R_7, and R_8 are hydrogen, in one embodiment R_6 and Q are independently pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_6 and Q, analogous to each and every combination of R_4 and Y_2 as set forth above, is specifically embraced by this latter embodiment.

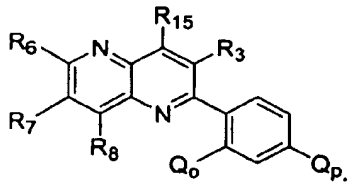
In one embodiment the compound has the structure



(XXIX)

Further according to this embodiment, in one embodiment each and every Q is Y_2.

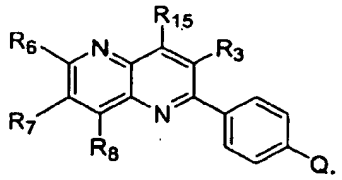
In one embodiment the compound has the structure



(XXXVI)

Further according to this embodiment, in one embodiment Q_p and Q_o are independently Y_2. Further according to this embodiment in which Q_p and Q_o are independently Y_2, in one embodiment R_3, R_{15}, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide. Further according to this embodiment in which Q_p and Q_o are independently Y_2, in one embodiment R_3, R_{15}, R_6, R_7, and R_8 are hydrogen. Further still according to this embodiment in which Q_p and Q_o are independently Y_2 and R_3, R_{15}, R_6, R_7, and R_8 are hydrogen, in one embodiment Q_p is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which Q_p and Q_o are independently Y_2 and R_3, R_{15}, R_6, R_7, and R_8 are hydrogen, in one embodiment Q_o is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which Q_p and Q_o are independently Y_2 and R_{15}, R_5, R_6, R_7, and R_8 are hydrogen, in one embodiment Q_p and Q_o are independently pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of Q_p and Q_o, analogous to each and every combination of R_4 and Y_2 as set forth above, is specifically embraced by this this latter embodiment.

In one embodiment the compound has the structure



(XXXVII)

Further according to this embodiment, in one embodiment R_6 is Y_2. Further according to this embodiment in which R_6 is Y_2, in one embodiment Q is independently Y_2. Further still according to this embodiment in which R_6 is Y_2 and Q is independently Y_2, in one embodiment R_3, R_{15}, R_7, and R_8 are hydrogen. Further still according to this embodiment in which R_6 is Y_2, Q is independently Y_2, and R_3, R_{15}, R_7, and R_8 are hydrogen, in one embodiment R_6 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 is Y_2, Q is independently Y_2, and R_3, R_{15}, R_7, and R_8 are hydrogen, in one embodiment R_6 is pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Further still according to this embodiment in which R_6 and Q are independently Y_2, and R_3, R_{15}, R_7, and R_8 are hydrogen, in one embodiment R_6 and Q are independently pip, diamine, dipamine, dimor, dipmor, dipip, or dippip. Each and every combination of R_6 and Q, analogous to each and every combination of R_4 and Y_2 as set forth above, is specifically embraced by this latter embodiment.

In one aspect the invention is a pharmaceutical composition. The pharmaceutical composition includes at least one compound of the invention, or a pharmaceutically acceptable salt of at least one compound of the invention, and a pharmaceutically acceptable carrier. In one embodiment the pharmaceutical composition is formulated for oral administration. In one embodiment the pharmaceutical composition is formulated for parenteral administration.

In one aspect the invention is a method for reducing signaling by a Toll-like receptor (TLR). The method according to this aspect of the invention includes the step of contacting a cell expressing a TLR, selected from TLR7, TLR8, and TLR9, with an effective amount of a composition of the invention to reduce signaling by the TLR in response to an agonist of the TLR, compared to signaling by the TLR in response to the agonist in absence of the contacting.

In one embodiment the TLR is TLR7. In one embodiment the TLR is TLR8. In one embodiment the TLR is TLR9. In one embodiment the TLR is a human TLR.

In one embodiment the agonist of the TLR is a CpG nucleic acid. In one embodiment the the agonist of the TLR is RNA.

In one embodiment the contacting occurs *in vitro*.

In one embodiment the cell expressing the TLR is an immune cell. In one embodiment the cell expressing the TLR is a cell that is modified to express the TLR.

In one aspect the invention is a method for reducing an immune response. The method according to this aspect of the invention includes the step of contacting a population of immune cells expressing a Toll-like receptor (TLR), selected from TLR7, TLR8, and TLR9, with an effective amount of a composition of the invention to reduce an immune response by the immune cells, compared to an immune response by the immune cells in absence of the contacting.

In one embodiment the TLR is TLR7. In one embodiment the TLR is TLR8. In one embodiment the TLR is TLR9. In one embodiment the TLR is a human TLR.

In one embodiment the contacting occurs *in vitro*. In one embodiment the contacting occurs *in vivo*.

In one embodiment the the immune response is a Th1-like immune response. In one embodiment the immune response is secretion of a cytokine. In one embodiment the immune response is secretion of a chemokine.

In one embodiment the immune response is an immune response to an antigen. In one embodiment the antigen is an allergen. In one embodiment the antigen is a microbial antigen. In one embodiment the antigen is an antigen characteristic of an autoimmune condition.

In one aspect the invention is a method for treating an autoimmune condition in a subject. The method includes the step of administering to a subject having an autoimmune condition, wherein the autoimmune condition involves signaling by a Toll-like receptor (TLR) selected from TLR7, TLR8, and TLR9, an effective amount of a composition of the invention to treat the autoimmune condition.

In one embodiment the TLR is TLR7. In one embodiment the TLR is TLR8. In one embodiment the TLR is TLR9. In one embodiment the TLR is a human TLR.

In one embodiment the autoimmune condition is selected from ankylosing spondylitis, atherosclerosis, autoimmune chronic active hepatitis, autoimmune encephalomyelitis, autoimmune hemolytic anemia, autoimmune thrombocytopenic

purpura, autoimmune-associated infertility, Behçet's syndrome, bullous pemphigoid, Churg-Strauss disease, Crohn's disease, glomerulonephritis, Goodpasture's syndrome, Grave's disease, Guillain-Barré syndrome, Hashimoto's thyroiditis, idiopathic Addison's disease, insulin-dependent diabetes mellitus, insulin resistance, mixed connective tissue disease, multiple sclerosis, myasthenia gravis, pemphigus, pernicious anemia, polyarteritis nodosa, polymyositis, primary biliary sclerosis, psoriasis, rheumatoid arthritis, sarcoidosis, scleroderma, sclerosing cholangitis, Sjögren's syndrome, systemic lupus erythematosus, Takayasu's arteritis, temporal arteritis, ulcerative colitis, and Wegener's granulomatosis.

In one embodiment the autoimmune condition is systemic lupus erythematosus.

In one embodiment the autoimmune condition is rheumatoid arthritis.

In one embodiment the subject is a human.

Each of the limitations of the invention can encompass various embodiments of the invention. It is, therefore, anticipated that each of the limitations of the invention involving any one element or combinations of elements can be included in each aspect of the invention. This invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having," "containing", "involving", and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

DETAILED DESCRIPTION OF THE INVENTION

The invention is based at least in part on the discovery by the inventors of certain small molecules that can inhibit signaling by Toll-like receptors (TLRs) and so inhibit an immune response. The compositions and methods of the invention can be used to inhibit immune responses, e.g., unwanted immune responses such as are involved in a variety of conditions and diseases characterized by antigen-specific or

antigen-nonspecific immune responses. Such conditions and diseases include, without limitation, autoimmune disorders, inflammation, and transplant rejection. Thus the invention relates at least in part to novel compositions and methods for their use in the treatment of diseases and disorders characterized by unwanted immune responses, including autoimmune disorders, inflammation, and transplant rejection.

Significantly, the compositions and methods of the invention can be used either with or without knowledge of the particular antigen or antigens that may be involved in an immune response. The compounds discovered according to the invention are inhibitors of one or more so-called pattern recognition receptors (PRRs) that signal immune cells in response to their interaction with particular nucleic acid molecules. Alternatively or in addition, the compounds discovered according to the invention are inhibitors of one or more so-called pattern recognition receptors (PRRs) that signal immune cells in response to their interaction with nucleic acid molecule-containing complexes, e.g., certain immune complexes. Of particular interest in connection with the instant invention are TLR7, TLR8, and TLR9, PRRs for certain nucleic acid molecules.

TLR7 interacts with single- and double-stranded RNA in a sequence-dependent manner, as well as with the imidazoquinolines imiquimod (R837) and resiquimod (R848). Heil F et al. (2004) *Science* 303:1526-9. In humans TLR7 is expressed in B cells and both myeloid dendritic cells (mDC) and plasmacytoid dendritic cells (pDC). In mice TLR7 is expressed in pDC.

TLR8 interacts with single-stranded RNA in a sequence-dependent manner, as well as with the imidazoquinolines imiquimod (R837) and resiquimod (R848). Heil F et al. (2004) *Science* 303:1526-9. In humans TLR8 is expressed in myeloid cells, but TLR8 is not expressed in mice.

TLR9 interacts with DNA containing CpG motifs that include unmethylated 5' cytosine-guanine 3' (CG) dinucleotides occurring within a the context of certain short flanking nucleotide sequences. Hemmi H et al. (2000) Nature 408:740-5. In humans TLR9 is expressed in B cells and pDC. In mice, TLR9 is expressed in B cells, pDC, and mDC.

As used herein, the term "CpG DNA" refers to an immunostimulatory nucleic acid which contains a cytosine-guanine (CG) dinucleotide, the C residue of which is

unmethylated. The effects of CpG nucleic acids on immune modulation have been described extensively in U.S. patents such as U.S. Pat. Nos. 6,194,388; 6,207,646; 6,239,116; and 6,218,371, and published international patent applications, such as WO98/37919, WO98/40100, WO98/52581, and WO99/56755. The entire contents of each of these patents and published patent applications is hereby incorporated by reference. The entire immunostimulatory nucleic acid can be unmethylated or portions may be unmethylated but at least the C of the 5'-CG-3' must be unmethylated.

CpG DNA includes both naturally occurring immunostimulatory nucleic acids, as found in bacterial DNA and plasmids, as well as synthetic oligodeoxynucleotides (ODN).

In one embodiment the CpG DNA is a CpG ODN that has a base sequence provided by 5'- TCGTCGTTTTGTCGTTTTGTCGTT -3' (ODN 2006; SEQ ID NO:1).

CpG ODN have been further classified by structure and function into at least the following three classes or types, all of which are intended to be encompassed within the term CpG DNA as used herein: B-class CpG ODN such as ODN 2006 include the originally described immunostimulatory CpG ODN and characteristically activate B cells and NK cells but do not induce or only weakly induce expression of type I interferon (e.g., IFN-α). A-class CpG ODN, described in published PCT international application WO 01/22990, incorporate a CpG motif, include a chimeric phosphodiester/phosphorothioate backbone, and characteristically activate NK cells and induce plasmacytoid dendritic cells to express large amounts of IFN-α but do not activate or only weakly activate B cells. An example of an A-class CpG ODN is 5'-G*G*G_G_G_A_C_G_A_T_C_G_T_C_G*G*G*G*G*G-3' (ODN 2216, SEQ ID NO:2), wherein "*" represents phosphorothioate and "_" represents phosphodiester. C-class CpG ODN incorporate a CpG, include a wholly phosphorothioate backbone, include a GC-rich palindromic or nearly-palindromic region, and are capable of both activating B cells and inducing expression of IFN-α. C-class CpG ODN have been described, for example, in published U.S. patent application 2003/0148976. An example of a C-class CpG ODN is 5'-TCGTCGTTTTCGGCGCGCGCCG-3' (ODN

2395; SEQ ID NO:3). For a review of the various classes of CpG ODN, see also Vollmer J et al. (2004) *Eur J Immunol* 34:251-62.

TLR7, TLR8, and TLR9 are characteristically expressed in endosomes of these particular classes of immune cells, and they are known to be inhibited by certain compounds, including in particular chloroquine and derivatives thereof, that are concentrated in endosomes.

A number of publications have described small molecule inhibitors of TLR9. These include US Patent Nos. 6,221,882, 6,399,630, 6,479,504, 6,521,637, and US Patent Application Publication Nos. 2003-0232856 and 2005-0119273, the entire contents of which are incorporated herein by reference. The inhibitor molecules disclosed in these patents and published patent applications include certain 4-aminoquinolines, 9-aminoacridines, 4-aminoquinazolines, and others, all of which are to be distinguished from the compositions disclosed herein.

The instant invention is based in part on the use of molecular modeling to perform a systematic study of predicted inhibitory activities of two-ringed core compounds substituted with any of a number of particular side group substituents. The modeling method provides a quantitative prediction of IC_{50} for a given compound, that is, the concentration required for half-maximal inhibition of immunostimulation induced by a stimulatory amount or concentration of suitable agonist. In one embodiment the IC_{50} is the concentration required for half-maximal inhibition of immunostimulation induced by EC_{50} of suitable agonist, e.g., CpG DNA for TLR9. The EC_{50} of an agonist is the concentration of agonist required for half-maximal stimulation by that agonist. A typical EC_{50} value for CpG DNA in respect of TLR9 is about 1 μM. In general, compounds with lower IC_{50} values are preferred over compounds with higher IC_{50} values. Predicted IC_{50} values for many compounds of interest typically fall within the range of less than 1 nM to about 2000 nM. Many compounds of interest have predicted IC_{50} values of less than or equal to about 500 nM, including, more particularly, those with predicted IC_{50} values of less than or equal to about 100 nM. As disclosed in the examples herein, many compounds of particular interest have predicted IC_{50} values of less than or equal to about 50 nM. Also as disclosed in the examples herein, many compounds of particular interest have

predicted IC_{50} values of less than or equal to about 30 nM. At least some compounds of particular interest have predicted IC_{50} values of less than or equal to about 1 nM.

Compounds identified by their predicted IC_{50} values can be evaluated for their potential as immunoinhibitory compounds and therapeutic agents. As disclosed herein, a candidate compound can be selected on the basis of its predicted IC_{50} value and tested in vitro to determine a corresponding actual in vitro IC_{50} value. Similarly, a candidate compound can be selected on the basis of its predicted IC_{50} value and tested in vivo to determine a corresponding actual in vivo IC_{50} value. Compounds with lower predicted IC_{50} values can be selected for in vitro and in vivo evaluation ahead of other compounds with higher predicted IC_{50} values. Generally compounds with lower actual IC_{50} values can be selected for further evaluation and development. Additional factors such as toxicity and solubility may be assessed in order to help select particular compounds for further development.

Particularly for clinical use, the invention embraces both the compounds alone as disclosed herein, as well as pharmaceutically acceptable salts thereof. The compounds of the invention, including pharmaceutically acceptable salts thereof, can be placed in pharmaceutically acceptable carriers to make pharmaceutical compositions. The compounds and compositions of the invention optionally can in addition be used or presented in combination with at least one other pharmaceutically active agent.

Also embraced by the instant invention are stereoisomers of the compounds as disclosed herein.

Compounds of the invention generally have certain core structures characterized by a two-ringed system, variously and optionally substituted in specified positions with particular substituents, as disclosed herein as structural formulas I – XXXVII. In addition to those compounds disclosed on the basis of their broader structural formulas and descriptions, nonlimiting embodiments of specific compounds according to the invention are disclosed in the examples below.

As used herein, the term "alkyl" is recognized in the art and may include saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight chain or

branched chain alkyl has about 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chain, C_3-C_{30} for branched chain), and alternatively, about 20 or fewer. Likewise, cycloalkyls have from about 3 to about 10 carbon atoms in their ring structure, and alternatively about 5, 6 or 7 carbons in the ring structure. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, cyclopentyl, cyclohexyl, and the like.

As used herein, the term "alkoxy" shall refer to the group -O-alkyl.

As used herein, the term "halide" is given its ordinary meaning in the art and shall refer to a fluorine, chlorine, bromine, or iodine atom.

As used herein, the term "heterocycle" is recognized in the art and shall refer to 3- to about 10-membered ring structures, such as 3- to about 7-membered rings, whose ring structures include one to four heteroatoms. Heterocycles may also be polycycles. Examples of heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like.

As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds, "permissible" being in the context of the chemical rules of valence known to those of ordinary skill in the art. In some cases, "substituted" may generally refer to replacement of a hydrogen with a substituent as described herein. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, include those described herein. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which

satisfy the valencies of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds. Examples of substituents include, but are not limited to, lower alkyl, lower aryl, lower aralkyl, lower cyclic alkyl, lower heterocycloalkyl, hydroxy, lower alkoxy, lower aryloxy, perhaloalkoxy, aralkoxy, lower heteroaryl, lower heteroaryloxy, lower heteroarylalkyl, lower heteroaralkoxy, azido, amino, halogen, lower alkylthio, oxo, lower acylalkyl, lower carboxy esters, carboxyl, -carboxamido, nitro, lower acyloxy, lower aminoalkyl, lower alkylaminoaryl, lower alkylaryl, lower alkylaminoalkyl, lower alkoxyaryl, lower arylamino, lower aralkylamino, lower alkylsulfonyl, lower -carboxamidoalkylaryl, lower -carboxamidoaryl, lower hydroxyalkyl, lower haloalkyl, lower alkylaminoalkylcarboxy-, lower aminocarboxamidoalkyl-, cyano, lower alkoxyalkyl, lower perhaloalkyl, lower arylalkyloxyalkyl, and the like.

As used herein, the term "optionally substituted", as used in reference to a particular class of chemical substituent, shall refer both to the unsubstituted form of the substituent and to a substituted form of the substituent. For example, the phrase "optionally substituted alkyl" refers both to alkyl and to substituted alkyl.

As used herein, the terms "nitrogen" and, equivalently, "N", refer to a nitrogen atom.

As used herein, the terms "oxygen" and, equivalently, "O", refer to an oxygen atom.

As used herein, the terms "hydrogen" and, equivalently, "H", refer to a hydrogen atom.

The invention in one aspect relates to a method for reducing signaling by a TLR selected from TLR7, TLR8, and TLR9. Each of these TLRs induces one or more intracellular signaling pathways as a consequence of interaction with a suitable agonist, e.g., a natural ligand. The signaling normally leads eventually to activation of at least one gene or at least one protein. In one embodiment a protein activated by a TLR signaling pathway is NF-κB. Activated NF-κB is a ubiquitous transcription factor that binds to promoters of a variety of genes involved in immune cell activation, thereby stimulating transcription of these genes.

In addition to its ability to stimulate expression of endogenous genes, activated NF-κB can also stimulate expression of suitable NF-κB-sensitive exogenous genes

such as reporter constructs well known in the art and described herein. A common NF-κB-sensitive reporter construct is based on a luciferase gene placed under the control of an NF-κB-sensitive promoter. When introduced into a suitable host cell, and in the presence of activated NF-κB, this reporter construct directs the expression in the cell of luciferase, a luminescent protein that can be conveniently and quantitatively assayed by measurement, at an appropriate wavelength, of light emitted by the expressed luciferase protein. Thus signaling by a TLR selected from TLR7, TLR8, and TLR9 can be measured, for example, by measuring NF-κB activation, either directly or indirectly, such as through measurement of an expressed product of an NF-κB-driven endogenous gene or NF-κB-driven reporter (e.g., luciferase).

The method results in a reduced level of signaling by the TLR in response to an agonist of the TLR as compared to a control level of signaling by the TLR in response to the agonist of the TLR. A control level of signaling is that level of signaling in response to the agonist of the TLR that occurs in absence of contacting a cell expressing the TLR with a compound or composition of the invention. For purposes of comparing treatment and control amounts of signaling, conditions are generally selected such that the number or concentration of TLR-expressing cells, the amount or concentration of the TLR agonist, temperature, and other such variables are identical or at least comparable between treatment and control measurements, so as to isolate the effect of the composition of the invention. Treatment and control measurements can be made in parallel or they can be made independently. For example, in one embodiment the control is a historical control. In one embodiment the control is a concurrent, parallel control.

Signaling is reduced whenever it is measurably less than a corresponding control amount of signaling. In various separate embodiments the reduced signaling is at least 5 percent, at least 10 percent, at least 15 percent, at least 20 percent, at least 25 percent, at least 30 percent, at least 40 percent, and at least 50 percent less than control. In other words, in various separate embodiments the reduced signaling is less than or equal to 95 percent, less than or equal to 90 percent, less than or equal to 85 percent, less than or equal to 80 percent, less than or equal to 75 percent, less than or equal to 70 percent, less than or equal to 60 percent, and less than or equal to 50 percent of control.

The method involves contacting a cell expressing the TLR, or a population of cells expressing the TLR, with a compound or composition of the invention. As used herein, a "cell expressing a TLR" refers to any cell which expresses, either naturally or artificially, a functional TLR. A functional TLR is a full-length TLR protein or a fragment thereof capable of inducing a signal in response to interaction with its ligand. Generally the functional TLR will include at least a TLR ligand-binding fragment of the extracellular domain of the full-length TLR and at least a fragment of a TIR domain capable of interacting with another Toll homology domain-containing polypeptide, e.g., MyD88. In various embodiments the functional TLR is a full-length TLR selected from TLR7, TLR8, and TLR9.

In one embodiment a cell expressing the TLR is a cell that naturally expressed the TLR.

In one embodiment a cell that naturally expresses TLR9 is a cell from human multiple myeloma cell line RPMI 8226 (ATCC CCL-155, American Type Culture Collection, Manassas, VA). This cell line was established from the peripheral blood of a 61-year-old man at the time of diagnosis of multiple myeloma (IgG lambda type). Matsuoka Y et al. (1967) *Proc Soc Exp Biol Med* 125:1246-50. RPMI 8226 was previously reported as responsive to CpG nucleic acids as evidenced by the induction of IL-6 protein and IL-12p40 mRNA. Takeshita F et al. (2000) *Eur J Immunol* 30:108-16; Takeshita F et al. (2000) *Eur J Immunol* 30:1967-76. Takeshita et al. used the cell line solely to study promoter constructs in order to identify transcription factor binding sites important for CpG nucleic acid signaling. It is now known that RPMI 8226 cells secrete a number of other chemokines and cytokines including IL-8, IL-10 and IP-10 in response to immunostimulatory nucleic acids. Because this cell line expresses TLR9, through which immunostimulatory nucleic acids such as for example CpG nucleic acids mediate their effects, it is a suitable cell line for use in the methods of the invention relating to reducing signaling by human TLR9.

Similar to peripheral blood mononuclear cells (PBMCs), the RPMI 8226 cell line has been observed to upregulate its cell surface expression of markers such as CD71, CD86 and HLA-DR in response to CpG nucleic acid exposure. This has been observed by flow cytometric analysis of the cell line. Accordingly, the methods provided herein can be structured to use appropriately selected cell surface marker

expression as a readout, in addition to or in place of chemokine or cytokine production or other readouts described elsewhere herein.

The RPMI 8226 cell line has also been found to respond to certain small molecules including imidazoquinoline compounds. For example, incubation of RPMI 8226 cells with the imidazoquinoline compound R848 (resiquimod) induces IL-8, IL-10, and IP-10 production. It has recently been reported that R848 mediates its immunostimulatory effects through TLR7 and TLR8. The ability of RPMI 8226 to respond to R848 suggests that the RPMI 8226 cell line also expresses TLR7, as previously reported for normal human B cells.

The RPMI cell line can be used in unmodified form or in a modified form. In one embodiment, the RPMI 8226 cell is transfected with a reporter construct. Preferably, the cell is stably transfected with the reporter construct. The reporter construct generally includes a promoter, a coding sequence and a polyadenylation signal. The coding sequence can include a reporter sequence selected from the group consisting of an enzyme (e.g., luciferase, alkaline phosphatase, beta-galactosidase, chloramphenicol acetyltransferase (CAT), secreted alkaline phosphatase, etc.), a bioluminescence marker (e.g., green fluorescent protein (GFP, U.S. Pat. No. 5,491,084), etc.), a surface-expressed molecule (e.g., CD25), a secreted molecule (e.g., IL-8, IL-12 p40, TNF-α, etc.), and other detectable protein products known to those of skill in the art. Preferably, the coding sequence encodes a protein having a level or an activity that is quantifiable.

In certain embodiments the TLR is artificially expressed (including over-expressed) by a cell, for example by introduction into the cell of an expression vector bearing a coding sequence for the TLR wherein the coding sequence is operably linked to a gene expression sequence. As used herein, a coding sequence and a gene expression sequence are said to be operably linked when they are covalently linked in such a way as to place the expression or transcription and/or translation of the coding sequence under the influence or control of the gene expression sequence. Two DNA sequences are said to be operably linked if induction of a promoter in the 5' gene expression sequence results in the transcription of the coding sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter

region to direct the transcription of the coding sequence, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a gene expression sequence would be operably linked to a coding sequence if the gene expression sequence were capable of effecting transcription of that coding sequence such that the resulting transcript is translated into the desired protein or polypeptide.

As noted above, in one embodiment a coding sequence includes a coding sequence for a TLR. In another embodiment a coding sequence includes a coding sequence for a reporter, e.g. luciferase.

A cell that artificially expresses a TLR can be a cell that does not express the TLR but for the TLR expression vector. For example, human 293 fibroblasts (ATCC CRL-1573) do not express TLR7, TLR8, or TLR9. Such cells can be transiently or stably transfected with a suitable expression vector (or vectors) so as to yield cells that express TLR7, TLR8, TLR9, or any combination thereof. Alternatively, a cell that artificially expresses a TLR can be a cell that expresses the TLR at a significantly higher level with the TLR expression vector than it does without the TLR expression vector.

Coding sequences for various TLRs of various species are known in the art and are available from public databases. For example, complementary DNA (cDNA) sequences for human and murine TLR7, TLR8, and TLR9 are all available from GenBank. These cDNA sequences and GenBank entries include and further specify coding sequences for each TLR.

In one embodiment a coding sequence for human TLR7 is provided as nucleotides 140 - 3289 in GenBank Accession No. NM_016562. In one embodiment a coding sequence for murine TLR7 is provided as nucleotides 49 - 3201 of GenBank Accession No. AY035889.

In one embodiment a coding sequence for human TLR8 is provided as nucleotides 49 - 3174 in GenBank Accession No. AF245703. In one embodiment a coding sequence for murine TLR8 is provided as nucleotides 59 - 3157 of GenBank Accession No. AY035890.

In one embodiment a coding sequence for human TLR9 is provided as nucleotides 145 - 3243 in GenBank Accession No. AF245704. In one embodiment a

coding sequence for murine TLR9 is provided as nucleotides 40 -3138 of GenBank Accession No. AF348140.

For use in the methods of the instant invention, a cell that artificially expresses a TLR is in one embodiment a stably transfected cell that expresses the TLR. Such a cell can also be stably transfected with a suitable reporter construct.

The invention in one aspect relates to a method for reducing an immune response. As used herein, an immune response refers to a response to an appropriate stimulus by a cell of the immune system, a population of cells of the immune system, or by an immune system. An immune system as used herein refers to an immune system of a mammal, specifically including but not limited to an immune system of a human.

A cell of an immune system can be any cell that is classified as an immune cell. Such cells include B cells, T cells, natural killer (NK) cells, mast cells, basophils, granulocytes, monocytes, macrophages, bone marrow-derived dendritic cells, and other professional antigen-presenting cells, as well as subcategories and precursors thereof. In one embodiment a cell of the immune system can be an isolated cell of the immune system.

A population of cells of the immune system refers to at least two cells, and more typically at least one thousand cells, of the immune system. In one embodiment a population of cells of the immune system can be an isolated population of cells of the immune system. In one embodiment a population of cells of the immune system is an isolated population of PBMC.

In one embodiment the method involves contacting a population of immune cells expressing a TLR selected from TLR7, TLR8, and TLR9, with a compound or composition of the invention. Immune cells that express TLR7, TLR8, or TLR9 can, but need not necessarily, be mutually exclusive. As mentioned above, immune cells expressing TLR7 can include B cells and dendritic cells, and immune cells expressing TLR8 can include myeloid cells. Also as mentioned above, immune cells expressing TLR9 can include B cells and pDC.

The method involves measuring a reduced immune response compared to a control immune response. A control immune response is an immune response that occurs in absence of contacting an immune cell, or a population of immune cells, with

a compound or composition of the invention. For purposes of comparing treatment and control immune responses, conditions are generally selected such that the number or concentration of TLR-expressing cells, the amount or concentration of the TLR agonist, temperature, and other such variables are identical or at least comparable between treatment and control measurements, so as to isolate the effect of the composition of the invention. Treatment and control measurements can be made in parallel or they can be made independently. For example, in one embodiment the control is a historical control. In one embodiment the control is a concurrent, parallel control.

An immune response is reduced whenever it is measurably less than the control immune response. In various separate embodiments the reduced immune response is at least 5 percent, at least 10 percent, at least 15 percent, at least 20 percent, at least 25 percent, at least 30 percent, at least 40 percent, and at least 50 percent less than control. In other words, in various separate embodiments the reduced immune response is less than or equal to 95 percent, less than or equal to 90 percent, less than or equal to 85 percent, less than or equal to 80 percent, less than or equal to 75 percent, less than or equal to 70 percent, less than or equal to 60 percent, and less than or equal to 50 percent of control.

In one embodiment the immune response is a Th1-like immune response. A Th1-like immune response refers to an immune response characterized by at least one feature characteristic of a Th1 immune response. In one embodiment a Th1-like immune response is a Th1 immune response. Features of a Th1 immune response can include secretion of one or more Th1 cytokines, immunoglobulin class switching to IgG1 (in humans) or IgG2a (in mice), and cell-mediated immunity. In contrast, features of a Th2 immune response can include secretion of one or more Th2 cytokines, immunoglobulin class switching to IgE (in humans and in mice) and IgG2 (in humans) or IgG1 (in mice), and humoral immunity.

As used herein, "cytokine" refers to any of a number of soluble proteins or glycoproteins that act on immune cells through specific receptors to affect the state of activation and function of the immune cells. Cytokines include interferons, interleukins, tumor necrosis factor, transforming growth factor beta, colony-stimulating factors (CSFs), chemokines, as well as others. Various cytokines affect

innate immunity, acquired immunity, or both. Cytokines specifically include, without limitation, IFN-α, IFN-β, IFN-γ, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12, IL-13, IL-18, TNF-α, TGF-β, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF). Chemokines specifically include, without limitation, IL-8, IP-10, I-TAC, RANTES, MIP-1α, MIP-1β, Gro-α, Gro-β, Gro-γ, MCP-1, MCP-2, and MCP-3.

Most mature $CD4^+$ T helper cells can be categorized into one of two cytokine-associated, cross-regulatory subsets or phenotypes: Th1 or Th2. Th1 cells are associated with IL-2, IL-3, IFN, GM-CSF, and high levels of TNF-α. Th2 cells are associated with IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, GM-CSF, and low levels of TNF-α. The Th1 subset promotes both cell-mediated immunity and humoral immunity that is characterized by immunoglobulin class switching to IgG2a in mice. Th1 responses can also be associated with delayed-type hypersensitivity and autoimmune disease. The Th2 subset induces primarily humoral immunity and induces immunoglobulin class switching to IgE and IgG1 in mice. The antibody isotypes associated with Th1 responses generally have good neutralizing and opsonizing capabilities, whereas those associated with Th2 responses are associated more with allergic responses.

Several factors have been shown to influence commitment to Th1 or Th2 profiles. The best characterized regulators are cytokines. IL-12 and IFN-γ are positive Th1 regulators and negative Th2 regulators. IL-12 promotes IFN-γ production, and IFN-γ provides positive feedback for IL-12. IL-4 and IL-10 appear to be required for the establishment of the Th2 cytokine profile and to down-regulate Th1 cytokine production; the effects of IL-4 are in some cases dominant over those of IL-12. IL-13 has been reported to inhibit expression of inflammatory cytokines, including IL-12 and TNF-α by LPS-induced monocytes, in a way similar to IL-4.

The method will generally further involve contacting the immune cells with an antigen, TLR agonist, or other stimulus normally involved inducing an immune response by the immune cells. The contacting in one embodiment can involve the step of adding or administering an antigen, TLR agonist, or other stimulus normally involved inducing an immune response by the immune cells. In one embodiment the contacting can entail passive exposure of the immune cells with an antigen, TLR

agonist, or other stimulus normally involved inducing an immune response by the immune cells. Passive contacting can occur, for example, in a subject having an autoimmune disease, inflammation, or transplant rejection.

In one embodiment the method relates to a method for reducing an immune response in a subject. As used herein, a subject refers to a mammal. In one embodiment the subject is a human. In another embodiment the subject is a non-human primate. In yet another embodiment the subject is a mammal other than a primate, including but not limited to a mouse, rat, hamster, guinea pig, rabbit, cat, dog, goat, sheep, pig, horse, or cow.

In one embodiment the immune response is an immune response to an antigen. As used herein, an antigen refers to any substance that induces an adaptive (specific) immune response. An antigen typically is any substance that can be specifically bound by a T-cell antigen receptor, antibody, or B-cell antigen receptor. Antigenic substances include, without limitation, peptides, proteins, carbohydrates, lipids, phospholipids, nucleic acids, autacoids, and hormones. Antigens specifically include allergens, autoantigens (i.e., self-antigens), cancer antigens, and microbial antigens. In respect of peptide antigens and protein antigens, antigens further include both antigens per se and nucleic acids encoding said antigens.

An allergen is a substance that can induce an allergic or asthmatic response in a susceptible subject. The list of allergens is enormous and can include pollens, insect venoms, animal dander, dust, fungal spores and drugs (e.g., penicillin). Examples of natural animal and plant allergens include proteins specific to the following genera: *Canis* (*Canis familiaris*); *Dermatophagoides* (e.g., *Dermatophagoides farinae*); *Felis* (e.g., *Felis domesticus*); *Ambrosia* (e.g., *Ambrosia artemuisfolia*); *Lolium* (e.g., *Lolium perenne* and *Lolium multiflorum*); *Cryptomeria* (e.g., *Cryptomeria japonica*); *Alternaria* (e.g., *Alternaria alternata*); *Alder*; *Alnus* (e.g., *Alnus gultinosa*); *Betula* (e.g., *Betula verrucosa*); *Quercus* (e.g., *Quercus alba*); *Olea* (e.g., *Olea europa*); *Artemisia* (e.g., *Artemisia vulgaris*); *Plantago* (e.g., *Plantago lanceolata*); *Parietaria* (e.g., *Parietaria officinalis* and *Parietaria judaica*); *Blattella* (e.g., *Blattella germanica*); *Apis* (e.g., *Apis multiforum*); *Cupressus* (e.g., *Cupressus sempervirens*, *Cupressus arizonica*, and *Cupressus macrocarpa*); *Juniperus* (e.g., *Juniperus sabinoides*, *Juniperus virginiana*, *Juniperus communis*, and *Juniperus ashei*); *Thuya*

(e.g., *Thuya orientalis*); *Chamaecyparis* (e.g., *Chamaecyparis obtusa*); *Periplaneta* (e.g., *Periplaneta americana*); *Agropyron* (e.g., *Agropyron repens*); *Secale* (e.g., *Secale cereale*); *Triticum* (e.g., *Triticum aestivum*); *Dactylis* (e.g., *Dactylis glomerata*); *Festuca* (e.g., *Festuca elatior*); *Poa* (e.g., *Poa pratensis* and *Poa compressa*); *Avena* (e.g., *Avena sativa*); *Holcus* (e.g., *Holcus lanatus*); *Anthoxanthum* (e.g., *Anthoxanthum odoratum*); *Arrhenatherum* (e.g., *Arrhenatherum elatius*); *Agrostis* (e.g., *Agrostis alba*); *Phleum* (e.g., *Phleum pratense*); *Phalaris* (e.g., *Phalaris arundinacea*); *Paspalum* (e.g., *Paspalum notatum*); *Sorghum* (e.g., *Sorghum halepensis*); and *Bromus* (e.g., *Bromus inermis*). The term "allergy' refers to acquired hypersensitivity to a substance (allergen). An "allergic reaction" is the response of an immune system to an allergen in a subject allergic to the allergen. Allergic conditions include eczema, allergic rhinitis or coryza, hay fever, bronchial asthma, urticaria (hives) and food allergies, and other atopic conditions.

Autoantigens include any antigen of host origin, but they specifically include antigens characteristic of an autoimmune disease or condition. Autoantigens characteristic of an autoimmune disease or condition can be associated with, but not necessarily established as causative of, an autoimmune disorder. Specific examples of autoantigens characteristic of an autoimmune disease or condition include but are not limited to insulin, thyroglobulin, glomerular basement membrane, acetylcholine receptor, DNA, and myelin basic protein.

A cancer antigen as used herein is a compound, such as a peptide or protein, associated with a tumor or cancer cell surface and which is capable of provoking an immune response when expressed on the surface of an antigen-presenting cell in the context of a major histocompatibility complex (MHC) molecule. Cancer antigens can be prepared from cancer cells either by preparing crude extracts of cancer cells, for example, as described in Cohen PA et al. (1994) *Cancer Res* 54:1055-8, by partially purifying the antigens, by recombinant technology, or by de novo synthesis of known antigens. Cancer antigens include but are not limited to antigens that are recombinantly expressed, an immunogenic portion thereof, or a whole tumor or cancer cell. Such antigens can be isolated or prepared recombinantly or by any other means known in the art.

The terms "cancer antigen" and "tumor antigen" are used interchangeably and refer to antigens which are differentially expressed by cancer cells and can thereby be exploited in order to target cancer cells. Cancer antigens are antigens which can potentially stimulate apparently tumor-specific immune responses. Some of these antigens are encoded, although not necessarily expressed, by normal cells. These antigens can be characterized as those which are normally silent (i.e., not expressed) in normal cells, those that are expressed only at certain stages of differentiation and those that are temporally expressed such as embryonic and fetal antigens. Other cancer antigens are encoded by mutant cellular genes, such as oncogenes (e.g., activated ras oncogene), suppressor genes (e.g., mutant p53), fusion proteins resulting from internal deletions or chromosomal translocations. Still other cancer antigens can be encoded by viral genes such as those carried on RNA and DNA tumor viruses.

Examples of tumor antigens include MAGE, MART-1/Melan-A, gp100, Dipeptidyl peptidase IV (DPPIV), adenosine deaminase-binding protein (ADAbp), cyclophilin b, Colorectal associated antigen (CRC)--C017-1A/GA733, Carcinoembryonic Antigen (CEA) and its immunogenic epitopes CAP-1 and CAP-2, etv6, aml1, Prostate Specific Antigen (PSA) and its immunogenic epitopes PSA-1, PSA-2, and PSA-3, prostate-specific membrane antigen (PSMA), T-cell receptor/CD3-zeta chain, MAGE-family of tumor antigens (e.g., MAGE-A1, MAGE-A2, MAGE-A3, MAGE-A4, MAGE-A5, MAGE-A6, MAGE-A7, MAGE-A8, MAGE-A9, MAGE-A10, MAGE-A11, MAGE-A12, MAGE-Xp2 (MAGE-B2), MAGE-Xp3 (MAGE-B3), MAGE-Xp4 (MAGE-B4), MAGE-C1, MAGE-C2, MAGE-C3, MAGE-C4, MAGE-C5), GAGE-family of tumor antigens (e.g., GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, GAGE-8, GAGE-9), BAGE, RAGE, LAGE-1, NAG, GnT-V, MUM-1, CDK4, tyrosinase, p53, MUC family, HER2/neu, p21 ras, RCAS1, α-fetoprotein, E-cadherin, α-catenin, β-catenin and γ-catenin, p120ctn, gp100.sup.Pmel 117, PRAME, NY-ESO-1, cdc27, adenomatous polyposis coli protein (APC), fodrin, Connexin 37, Ig-idiotype, p15, gp75, GM2 and GD2 gangliosides, viral products such as human papillomavirus proteins, Smad family of tumor antigens, lmp-1, P1 A, EBV-encoded nuclear antigen (EBNA)-1, brain glycogen phosphorylase, SSX-1, SSX-2 (HOM-MEL-40), SSX-1, SSX-4, SSX-5, SCP-1 and CT-7, and c-erbB-2.

Cancers or tumors and tumor antigens associated with such tumors (but not exclusively), include acute lymphoblastic leukemia (etv6; aml1; cyclophilin b), B cell lymphoma (Ig-idiotype), glioma (E-cadherin; α-catenin; β-catenin; γ-catenin; p120ctn), bladder cancer (p21ras), biliary cancer (p21ras), breast cancer (MUC family; HER2/neu; c-erbB-2), cervical carcinoma (p53; p21ras), colon carcinoma (p21ras; HER2/neu; c-erbB-2; MUC family), colorectal cancer (Colorectal associated antigen (CRC)--C017-1A/GA733; APC), choriocarcinoma (CEA), epithelial cell cancer (cyclophilin b), gastric cancer (HER2/neu; c-erbB-2; ga733 glycoprotein), hepatocellular cancer (α-fetoprotein), Hodgkin's lymphoma (imp-1; EBNA-1), lung cancer (CEA; MAGE-3; NY-ESO-1), lymphoid cell-derived leukemia (cyclophilin b), melanoma (p115 protein, gp75, oncofetal antigen, GM2 and GD2 gangliosides), myeloma (MUC family; p21ras), non-small cell lung carcinoma (HER2/neu; c-erbB-2), nasopharyngeal cancer (Imp-1; EBNA-1), ovarian cancer (MUC family; HER2/neu; c-erbB-2), prostate cancer (Prostate Specific Antigen (PSA) and its immunogenic epitopes PSA-1, PSA-2, and PSA-3; prostate-specific membrane antigen (PSMA); HER2/neu; c-erbB-2), pancreatic cancer (p21ras; MUC family; HER2/neu; c-erbB-2; ga733 glycoprotein), renal cancer (HER2/neu; c-erbB-2), squamous cell cancers of cervix and esophagus (viral products such as human papillomavirus proteins), testicular cancer (NY-ESO-1), T-cell leukemia (HTLV-1 epitopes), and melanoma (Melan-A/MART-1; cdc27; MAGE-3; p21ras; gp100.sup.Pmel117).

A microbial antigen can be an antigen that is or is derived from an infectious microbial agent, including a bacterium, a virus, a fungus, or a parasite.

Examples of infectious bacteria include: *Helicobacter pylori*, *Borrelia burgdorferi*, *Legionella pneumophila*, *Mycobacteria* sps (such as. *M. tuberculosis*, *M. avium*, *M. intracellulare*, *M. kansasii*, and *M. gordonae*), *Staphylococcus aureus*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Listeria monocytogenes*, *Streptococcus pyogenes* (Group A Streptococcus), *Streptococcus agalactiae* (Group B Streptococcus), Streptococcus (viridans group), *Streptococcus faecalis*, *Streptococcus bovis*, Streptococcus (anaerobic sps.), *Streptococcus pneumoniae*, pathogenic *Campylobacter* sp., *Enterococcus* sp., *Haemophilus influenzae*, *Bacillus anthracis*, *Chlamydia trachomatis*, *Corynebacterium diphtheriae*, *Corynebacterium* sp.,

Erysipelothrix rhusiopathiae, *Clostridium perfringens*, *Clostridium tetani*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Pasturella multocida*, *Bacteroides* sp., *Fusobacterium nucleatum*, *Streptobacillus moniliformis*, *Treponema pallidum*, *Treponema pertenue*, *Leptospira*, and *Actinomyces israelii*.

Examples of infectious virus include: *Retroviridae* (including but not limited to human immunodeficiency virus (HIV)); *Picornaviridae* (for example, polio viruses, hepatitis A virus; enteroviruses, human coxsackie viruses, rhinoviruses, echoviruses); *Calciviridae* (such as strains that cause gastroenteritis); *Togaviridae* (for example, equine encephalitis viruses, rubella viruses); *Flaviviridae* (for example, dengue viruses, encephalitis viruses, yellow fever viruses); *Coronaviridae* (for example, coronaviruses); *Rhabdoviridae* (for example, vesicular stomatitis viruses, rabies viruses); *Filoviridae* (for example, ebola viruses); *Paramyxoviridae* (for example, parainfluenza viruses, mumps virus, measles virus, respiratory syncytial virus); *Orthomyxoviridae* (for example, influenza viruses); *Bunyaviridae* (for example, Hantaan viruses, bunya viruses, phleboviruses, and Nairo viruses); *Arenaviridae* (hemorrhagic fever viruses); *Reoviridae* (e.g., reoviruses, orbiviurses, and rotaviruses); *Birnaviridae*; *Hepadnaviridae* (Hepatitis B virus); *Parvoviridae* (parvoviruses); *Papovaviridae* (papilloma viruses, polyoma viruses); *Adenoviridae* (most adenoviruses); *Herpesviridae* (herpes simplex virus (HSV) 1 and HSV-2, varicella zoster virus, cytomegalovirus (CMV), herpes viruses); *Poxviridae* (variola viruses, vaccinia viruses, pox viruses); and *Iridoviridae* (such as African swine fever virus); and unclassified viruses (for example, the etiological agents of spongiform encephalopathies, the agent of delta hepatitis (thought to be a defective satellite of hepatitis B virus), the agents of non-A, non-B hepatitis (class 1=internally transmitted; class 2=parenterally transmitted (i.e., Hepatitis C); Norwalk and related viruses, and astroviruses).

Examples of infectious fungi include, but are not limited to, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, and *Candida albicans*.

The invention in one aspect relates to a method for treating an autoimmune condition in a subject. As used herein, an autoimmune condition refers to an

autoimmune disease or disorder, i.e., an immunologically mediated acute or chronic process, directed by immune cells of a host subject against a tissue or organ of the host subject, resulting in injury to the tissue or organ. The term encompasses both cellular and antibody-mediated autoimmune phenomena, as well as organ-specific and organ-nonspecific autoimmunity.

Autoimmune conditions specifically include insulin-dependent diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus (SLE), multiple sclerosis, atherosclerosis, and inflammatory bowel disease. Inflammatory bowel disease includes Crohn's disease and ulcerative colitis. Autoimmune diseases also include, without limitation, ankylosing spondylitis, autoimmune chronic active hepatitis, autoimmune encephalomyelitis, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, autoimmune-associated infertility, Behçet's syndrome, bullous pemphigoid, Churg-Strauss disease, glomerulonephritis, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome, Hashimoto's thyroiditis, idiopathic Addison's disease, idiopathic thrombocytopenia, insulin resistance, mixed connective tissue disease, myasthenia gravis, pemphigus, pernicious anemia, polyarteritis nodosa, polymyositis/dermatomyositis, primary biliary sclerosis, psoriasis, Reiter's syndrome, sarcoidosis, sclerosing cholangitis, Sjögren's syndrome, systemic sclerosis (scleroderma and CREST syndrome), Takayasu's arteritis, temporal arteritis, and Wegener's granulomatosis. All of these entities are well known in the medical arts and need not be described further here.

The method of treatment of an autoimmune condition in a subject specifically includes treatment of a human subject. In one embodiment the autoimmune condition is systemic lupus erythematosus. In one embodiment the autoimmune condition is rheumatoid arthritis.

The method of treatment of an autoimmune condition in a subject optionally can further include administration of another treatment agent or treatment modality useful in the treatment of the autoimmune condition. For example, the method can include administration of a compound or composition of the invention, either alone or in combination with an agent such as a corticosteroid (e.g., prednisone), a cytokine (e.g., IFN-α), or other suitable immunomodulatory agent. In this context, "in combination with" can refer to simultaneous administration at a single site of

administration, or at different sites of administration. Alternatively and in addition, "in combination with" can refer to sequential administration at a single site of administration, or at different sites of administration.

As will be evident from the foregoing, autoimmune diseases also include certain immune complex-associated diseases. The term "immune complex-associated disease" as used herein refers to any disease characterized by the production and/or tissue deposition of immune complexes, including, but not limited to systemic lupus erythematosus (SLE) and related connective tissue diseases, rheumatoid arthritis, hepatitis C- and hepatitis B-related immune complex disease (e.g., cryoglobulinemia), Behçet's syndrome, autoimmune glomerulonephritides, and vasculopathy associated with the presence of LDL/anti-LDL immune complexes.

As used herein, the term "treat" as used in reference to a disorder, disease, or condition means to prevent or slow the development of the disorder, disease, or condition; to prevent, slow or halt the progression of the disorder, disease, or condition; and/or to eliminate the disorder, disease, or condition.

For purposes of description that follows, unless otherwise indicated or except as apparent from context, an "active agent" refers to a compound or composition of the invention, disclosed herein.

The term "effective amount" refers to the amount necessary or sufficient to realize a desired biologic effect. Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and preferred mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial toxicity and yet is effective to treat the particular subject. The effective amount for any particular application can vary depending on such factors as the disease or condition being treated, the particular active agent being administered, the size of the subject, or the severity of the disease or condition. One of ordinary skill in the art can empirically determine the effective amount of a particular active agent and/or other therapeutic agent without necessitating undue experimentation. It is preferred generally that a maximum dose be used, that is, the highest safe dose according to some medical judgment. Multiple doses per day may be contemplated to achieve appropriate systemic levels of

compounds. Appropriate system levels can be determined by, for example, measurement of the subject's peak or sustained plasma level of the active agent. "Dose" and "dosage" are used interchangeably herein.

Generally, daily oral doses of active compounds will be from about 0.01 milligrams/kg per day to 1000 milligrams/kg per day. It is expected that oral doses in the range of 0.5 to 50 milligrams/kg, in one or several administrations per day, will yield the desired results. Dosage may be adjusted appropriately to achieve desired drug levels, local or systemic, depending upon the mode of administration. For example, it is expected that intravenous administration would be from an order to several orders of magnitude lower dose per day. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Multiple doses per day are contemplated to achieve appropriate systemic levels of compounds.

For any compound described herein the therapeutically effective amount can be initially determined from animal models. A therapeutically effective dose can also be determined from human data for active agents which have been tested in humans and for compounds which are known to exhibit similar pharmacological activities, such as other related active agents. Higher doses may be required for parenteral administration. The applied dose can be adjusted based on the relative bioavailability and potency of the administered compound. Adjusting the dose to achieve maximal efficacy based on the methods described above and other methods as are well known in the art is well within the capabilities of the ordinarily skilled artisan.

The formulations of the invention are administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients.

For use in therapy, an effective amount of the active agent can be administered to a subject by any mode that delivers the active agent to the desired surface. Administering the pharmaceutical composition of the present invention may be accomplished by any means known to the skilled artisan. Preferred routes of administration include but are not limited to oral, parenteral, intravenous,

intramuscular, intraperitoneal, intranasal, sublingual, intratracheal, inhalation, ocular, vaginal, and rectal.

For oral administration, the compounds (i.e., active agents, and other therapeutic agents) can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained as solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Optionally the oral formulations may also be formulated in saline or buffers, e.g. EDTA for neutralizing internal acid conditions or may be administered without any carriers.

Also specifically contemplated are oral dosage forms of the above component or components. The component or components may be chemically modified so that oral delivery of the derivative is efficacious. Generally, the chemical modification contemplated is the attachment of at least one moiety to the component molecule itself, where said moiety permits (a) inhibition of proteolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the component or components and increase in circulation time in the body. Examples of such moieties include: polyethylene glycol, copolymers of ethylene glycol and propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinylpyrrolidone and polyproline. Abuchowski and Davis, 1981, "Soluble Polymer-Enzyme Adducts" In: *Enzymes as Drugs*, Hocenberg and Roberts, eds., Wiley-Interscience, New York, NY, pp. 367-383; Newmark, et al. (1982) *J. Appl. Biochem.* 4:185-189. Other polymers that could be used are poly-1,3-dioxolane and poly-1,3,6-

tioxocane. Preferred for pharmaceutical usage, as indicated above, are polyethylene glycol moieties.

For the component (or derivative) the location of release may be the stomach, the small intestine (the duodenum, the jejunum, or the ileum), or the large intestine. One skilled in the art has available formulations which will not dissolve in the stomach, yet will release the material in the duodenum or elsewhere in the intestine. Preferably, the release will avoid the deleterious effects of the stomach environment, either by protection of the active agent (or derivative) or by release of the biologically active material beyond the stomach environment, such as in the intestine.

To ensure full gastric resistance a coating impermeable to at least pH 5.0 is essential. Examples of the more common inert ingredients that are used as enteric coatings are cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), HPMCP 50, HPMCP 55, polyvinyl acetate phthalate (PVAP), Eudragit L30D, Aquateric, cellulose acetate phthalate (CAP), Eudragit L, Eudragit S, and Shellac. These coatings may be used as mixed films.

A coating or mixture of coatings can also be used on tablets, which are not intended for protection against the stomach. This can include sugar coatings, or coatings which make the tablet easier to swallow. Capsules may consist of a hard shell (such as gelatin) for delivery of dry therapeutic, e.g., powder; for liquid forms, a soft gelatin shell may be used. The shell material of cachets could be thick starch or other edible paper. For pills, lozenges, molded tablets or tablet triturates, moist massing techniques can be used.

The therapeutic can be included in the formulation as fine multi-particulates in the form of granules or pellets of particle size about 1 mm. The formulation of the material for capsule administration could also be as a powder, lightly compressed plugs or even as tablets. The therapeutic could be prepared by compression.

Colorants and flavoring agents may all be included. For example, the active agent (or derivative) may be formulated (such as by liposome or microsphere encapsulation) and then further contained within an edible product, such as a refrigerated beverage containing colorants and flavoring agents.

One may dilute or increase the volume of the therapeutic with an inert material. These diluents could include carbohydrates, especially mannitol, a-lactose, anhydrous

lactose, cellulose, sucrose, modified dextrans and starch. Certain inorganic salts may be also be used as fillers including calcium triphosphate, magnesium carbonate and sodium chloride. Some commercially available diluents are Fast-Flo, Emdex, STA-Rx 1500, Emcompress and Avicell.

Disintegrants may be included in the formulation of the therapeutic into a solid dosage form. Materials used as disintegrants include but are not limited to starch, including the commercial disintegrant based on starch, Explotab. Sodium starch glycolate, Amberlite, sodium carboxymethylcellulose, ultramylopectin, sodium alginate, gelatin, orange peel, acid carboxymethylcellulose, natural sponge and bentonite may all be used. Another form of the disintegrants are the insoluble cationic exchange resins. Powdered gums may be used as disintegrants and as binders and these can include powdered gums such as agar, Karaya or tragacanth. Alginic acid and its sodium salt are also useful as disintegrants.

Binders may be used to hold the therapeutic agent together to form a hard tablet and include materials from natural products such as acacia, tragacanth, starch and gelatin. Others include methyl cellulose (MC), ethyl cellulose (EC) and carboxymethylcellulose (CMC). Polyvinylpyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC) could both be used in alcoholic solutions to granulate the therapeutic.

An anti-frictional agent may be included in the formulation of the therapeutic to prevent sticking during the formulation process. Lubricants may be used as a layer between the therapeutic and the die wall, and these can include but are not limited to: stearic acid including its magnesium and calcium salts, polytetrafluoroethylene (PTFE), liquid paraffin, vegetable oils and waxes. Soluble lubricants may also be used such as sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol of various molecular weights, Carbowax 4000 and 6000.

Glidants that might improve the flow properties of the drug during formulation and to aid rearrangement during compression might be added. The glidants may include starch, talc, pyrogenic silica and hydrated silicoaluminate.

To aid dissolution of the therapeutic into the aqueous environment a surfactant might be added as a wetting agent. Surfactants may include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents might be used and could include benzalkonium chloride or

benzethonium chloride. Potential non-ionic detergents that could be included in the formulation as surfactants include lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50, and 60, glycerol monostearate, polysorbate 40, 60, 65, and 80, sucrose fatty acid ester, methyl cellulose and carboxymethylcellulose. These surfactants could be present in the formulation of the active agent or derivative either alone or as a mixture in different ratios.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Microspheres formulated for oral administration may also be used. Such microspheres have been well defined in the art. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Also contemplated herein is pulmonary delivery of the active agent (or derivative thereof). The active agent (or derivative) is delivered to the lungs of a mammal while inhaling and traverses across the lung epithelial lining to the blood stream. Other reports of inhaled molecules include Adjei et al. (1990) *Pharmaceutical Research* 7:565-569; Adjei et al. (1990) *International Journal of Pharmaceutics* 63:135-144

(leuprolide acetate); Braquet et al. (1989) *Journal of Cardiovascular Pharmacology* 13(suppl. 5):143-146 (endothelin-1); Hubbard et al. (1989) *Annals of Internal Medicine* 111:206-212 (α1- antitrypsin); Smith et al. (1989) *J. Clin. Invest.* 84:1145-1146 (α-1-proteinase inhibitor); Oswein et al., 1990, "Aerosolization of Proteins", Proceedings of Symposium on Respiratory Drug Delivery II, Keystone, Colorado, March, (recombinant human growth hormone); Debs et al. (1988) *J. Immunol.* 140:3482-3488 (interferon-γ and tumor necrosis factor alpha); and Platz et al., U.S. Patent No. 5,284,656 (granulocyte colony stimulating factor). A method and composition for pulmonary delivery of drugs for systemic effect is described in U.S. Patent No. 5,451,569, issued September 19, 1995 to Wong et al.

Contemplated for use in the practice of this invention are a wide range of mechanical devices designed for pulmonary delivery of therapeutic products, including but not limited to nebulizers, metered dose inhalers, and powder inhalers, all of which are familiar to those skilled in the art.

Some specific examples of commercially available devices suitable for the practice of this invention are the Ultravent nebulizer, manufactured by Mallinckrodt, Inc., St. Louis, Missouri; the Acorn II nebulizer, manufactured by Marquest Medical Products, Englewood, Colorado; the Ventolin metered dose inhaler, manufactured by Glaxo Inc., Research Triangle Park, North Carolina; and the Spinhaler powder inhaler, manufactured by Fisons Corp., Bedford, Massachusetts.

All such devices require the use of formulations suitable for the dispensing of active agent (or derivative). Typically, each formulation is specific to the type of device employed and may involve the use of an appropriate propellant material, in addition to the usual diluents, adjuvants and/or carriers useful in therapy. Also, the use of liposomes, microcapsules or microspheres, inclusion complexes, or other types of carriers is contemplated. Chemically modified active agent may also be prepared in different formulations depending on the type of chemical modification or the type of device employed.

Formulations suitable for use with a nebulizer, either jet or ultrasonic, will typically comprise active agent (or derivative) dissolved in water at a concentration of about 0.1 to 25 mg of biologically active active agent per ml of solution. The formulation may also include a buffer and a simple sugar (e.g., for active agent

stabilization and regulation of osmotic pressure). The nebulizer formulation may also contain a surfactant, to reduce or prevent surface induced aggregation of the active agent caused by atomization of the solution in forming the aerosol.

Formulations for use with a metered-dose inhaler device will generally comprise a finely divided powder containing the active agent (or derivative) suspended in a propellant with the aid of a surfactant. The propellant may be any conventional material employed for this purpose, such as a chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof. Suitable surfactants include sorbitan trioleate and soya lecithin. Oleic acid may also be useful as a surfactant.

Formulations for dispensing from a powder inhaler device will comprise a finely divided dry powder containing active agent (or derivative) and may also include a bulking agent, such as lactose, sorbitol, sucrose, or mannitol in amounts which facilitate dispersal of the powder from the device, e.g., 50 to 90% by weight of the formulation. The active agent (or derivative) should most advantageously be prepared in particulate form with an average particle size of less than 10 mm (or microns), most preferably 0.5 to 5 mm, for most effective delivery to the distal lung.

Nasal delivery of a pharmaceutical composition of the present invention is also contemplated. Nasal delivery allows the passage of a pharmaceutical composition of the present invention to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those with dextran or cyclodextran.

For nasal administration, a useful device is a small, hard bottle to which a metered dose sprayer is attached. In one embodiment, the metered dose is delivered by drawing the pharmaceutical composition of the present invention solution into a chamber of defined volume, which chamber has an aperture dimensioned to aerosolize and aerosol formulation by forming a spray when a liquid in the chamber is compressed. The chamber is compressed to administer the pharmaceutical composition of the present invention. In a specific embodiment, the chamber is a piston arrangement. Such devices are commercially available.

Alternatively, a plastic squeeze bottle with an aperture or opening dimensioned to aerosolize an aerosol formulation by forming a spray when squeezed is used. The opening is usually found in the top of the bottle, and the top is generally tapered to partially fit in the nasal passages for efficient administration of the aerosol formulation. Preferably, the nasal inhaler will provide a metered amount of the aerosol formulation, for administration of a measured dose of the drug.

The compounds, when it is desirable to deliver them systemically, may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethylcellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active compounds may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be formulated with suitable polymeric or hydrophobic materials (for example as an

emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Suitable liquid or solid pharmaceutical preparation forms are, for example, aqueous or saline solutions for inhalation, microencapsulated, encochleated, coated onto microscopic gold particles, contained in liposomes, nebulized, aerosols, pellets for implantation into the skin, or dried onto a sharp object to be scratched into the skin. The pharmaceutical compositions also include granules, powders, tablets, coated tablets, (micro)capsules, suppositories, syrups, emulsions, suspensions, creams, drops or preparations with protracted release of active compounds, in whose preparation excipients and additives and/or auxiliaries such as disintegrants, binders, coating agents, swelling agents, lubricants, flavorings, sweeteners or solubilizers are customarily used as described above. The pharmaceutical compositions are suitable for use in a variety of drug delivery systems. For a brief review of methods for drug delivery, see Langer (1990) *Science* 249:1527-1533, which is incorporated herein by reference.

The active agents and optionally other therapeutics may be administered *per se* (neat) or in the form of a pharmaceutically acceptable salt. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulphonic, tartaric, citric, methane sulphonic, formic, malonic, succinic, naphthalene-2-sulphonic, and benzene sulphonic. Also, such salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group.

Suitable buffering agents include: acetic acid and a salt (1-2% w/v); citric acid and a salt (1-3% w/v); boric acid and a salt (0.5-2.5% w/v); and phosphoric acid and a salt (0.8-2% w/v). Suitable preservatives include benzalkonium chloride (0.003-

0.03% w/v); chlorobutanol (0.3-0.9% w/v); parabens (0.01-0.25% w/v) and thimerosal (0.004-0.02% w/v).

The pharmaceutical compositions of the invention contain an effective amount of active agent and optionally therapeutic agents included in a pharmaceutically-acceptable carrier. The term pharmaceutically-acceptable carrier means one or more compatible solid or liquid filler, diluents or encapsulating substances which are suitable for administration to a human or other vertebrate animal. The term carrier denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being commingled with the compounds of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficiency.

In one embodiment the pharmaceutical composition is a sterile preparation containing the active agent. The composition can be made sterile by any suitable means, including filter sterilization.

The therapeutic agent(s), including specifically but not limited to the active agent, may be provided in particles. Particles as used herein means nano or microparticles (or in some instances larger) which can consist in whole or in part of the active agent or the other therapeutic agent(s) as described herein. The particles may contain the therapeutic agent(s) in a core surrounded by a coating, including, but not limited to, an enteric coating. The therapeutic agent(s) also may be dispersed throughout the particles. The therapeutic agent(s) also may be adsorbed into the particles. The particles may be of any order release kinetics, including zero order release, first order release, second order release, delayed release, sustained release, immediate release, and any combination thereof, etc. The particle may include, in addition to the therapeutic agent(s), any of those materials routinely used in the art of pharmacy and medicine, including, but not limited to, erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof. The particles may be microcapsules which contain the active agent in a solution or in a semi-solid state. The particles may be of virtually any shape.

Both non-biodegradable and biodegradable polymeric materials can be used in the manufacture of particles for delivering the therapeutic agent(s). Such polymers may be natural or synthetic polymers. The polymer is selected based on the period of time over which release is desired. Bioadhesive polymers of particular interest include bioerodible hydrogels described by H.S. Sawhney, C.P. Pathak and J.A. Hubell in *Macromolecules*, (1993) 26:581-587, the teachings of which are incorporated herein. These include polyhyaluronic acids, casein, gelatin, glutin, polyanhydrides, polyacrylic acid, alginate, chitosan, poly(methyl methacrylates), poly(ethyl methacrylates), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

The therapeutic agent(s) may be contained in controlled release systems. The term "controlled release" is intended to refer to any drug-containing formulation in which the manner and profile of drug release from the formulation are controlled. This refers to immediate as well as non-immediate release formulations, with non-immediate release formulations including but not limited to sustained release and delayed release formulations. The term "sustained release" (also referred to as "extended release") is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period. The term "delayed release" is used in its conventional sense to refer to a drug formulation in which there is a time delay between administration of the formulation and the release of the drug therefrom. "Delayed release" may or may not involve gradual release of drug over an extended period of time, and thus may or may not be "sustained release."

Use of a long-term sustained release implant may be particularly suitable for treatment of chronic conditions. "Long-term" release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 7 days, and preferably 30-60 days. Long-term sustained release implants are well-known to those of ordinary skill in the art and include some of the release systems described above.

The present invention is further illustrated by the following Examples, which in no way should be construed as further limiting. The entire contents of all of the references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated by reference.

EXAMPLES

Example 1

Predicted Activities for Compounds of Formula III

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula III wherein R_3, R_7, and R_8 are hydrogen, and R_6 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 1 below. In this set of data the compound with the lowest predicted IC_{50}, 33 nM, had R_4 = dipip and Y_2 = dippip.

Table 1

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	83	59	49	64	48	50	61
	diamine	150	56	47	45	64	48	49
	dipamine	59	120	74	75	86	48	79
	dimor	66	58	41	50	38	41	58
	dipmor	100	58	52	42	41	43	40
	dipip	69	41	36	57	39	50	33
	dippip	90	46	39	43	58	43	37

Example 2

Predicted Activities for Compounds of Formula III

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula III wherein R_3, R_6, and R_8 are hydrogen, and R_7 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 2 below. In this set of data the compound with the lowest predicted IC_{50}, 33 nM, had R_4 = diamine and Y_2 = dippip.

Table 2

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	67	77	76	75	73	84	91
	diamine	79	120	79	65	87	75	33
	dipamine	68	67	170	90	81	65	110
	dimor	65	79	82	83	68	66	36
	dipmor	64	75	90	87	79	77	90
	dipip	69	55	86	78	66	65	73
	dippip	75	73	75	63	72	84	85

Example 3

Predicted Activities for Compounds of Formula III

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula III wherein R_3, R_6, and R_7 are hydrogen, and R_8 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 3 below. In this set of data the compound with the lowest predicted IC_{50}, 51 nM, had R_4 = dimor and Y_2 = dipip.

Table 3

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	530	460	120	330	440	410	160
	diamine	100	98	78	66	88	83	82
	dipamine	96	88	82	78	76	91	72
	dimor	100	64	73	92	77	51	80
	dipmor	79	70	77	120	130	69	66
	dipip	94	75	68	77	78	110	76
	dippip	65	67	55	79	60	71	72

Example 4

Predicted Activities for Compounds of Formula III

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula III wherein R_6, R_7, and R_8 are hydrogen, and R_3 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in

Table 4 below. In this set of data the compound with the lowest predicted IC_{50}, 36 nM, had $R_4 = Y_2 =$ dipip.

Table 4

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	80	90	130	100	110	81	37
	diamine	54	100	71	110	220	43	49
	dipamine	140	98	150	44	220	400	290
	dimor	75	76	42	110	230	110	58
	dipmor	110	180	130	67	210	110	37
	dipip	70	50	64	110	150	36	54
	dippip	68	89	370	230	200	180	430

Example 5

Predicted Activities for Compounds of Formula III

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula III wherein R_3 and R_7 are hydrogen, R_6 is Y_2, and R_8 is Y_3 (unsubsituted phenyl). Substitutions for R_4 and Y_2 were made as shown in Table 5 below. In this set of data the compound with the lowest predicted IC_{50}, 31 nM, had $R_4 = Y_2 =$ dipip.

Table 5

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	1200	930	580	1100	650	880	760
	diamine	120	170	160	70	42	77	120
	dipamine	150	600	140	220	250	130	210
	dimor	250	130	97	110	72	110	140
	dipmor	430	430	470	490	460	430	190
	dipip	130	170	110	110	140	31	49
	dippip	830	120	200	400	280	390	460

Example 6

Predicted Activities for Compounds of Formula III

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula III wherein R_6 and R_8 are hydrogen, R_3 is Y_3 (unsubsituted phenyl), and R_7 is Y_2. Substitutions for R_4 and Y_2 were made as shown in Table 6 below. In this set of data the compound with the lowest predicted IC_{50}, 36 nM, had R_4 = pip and Y_2 = dippip.

Table 6

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	1200	63	42	770	120	63	36
	diamine	630	100	53	180	230	110	50
	dipamine	240	46	630	350	390	270	80
	dimor	750	87	220	140	45	130	210
	dipmor	320	63	82	1000	290	130	100
	dipip	530	100	190	360	110	69	210
	dippip	200	51	270	290	170	89	96

Example 7

Predicted Activities for Compounds of Formula IV

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula IV wherein R_7 and R_8 are hydrogen, and R_6 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 7 below. In this set of data the compound with the lowest predicted IC_{50}, 37 nM, had R_4 = Y_2 = diamine.

Table 7

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	73	120	110	87	220	95	240
	diamine	97	37	140	1000	140	320	600
	dipamine	100	120	920	140	400	820	100
	dimor	55	120	300	65	1300	89	760
	dipmor	91	85	110	460	260	160	92
	dipip	110	78	960	86	480	100	320
	dippip	290	250	1200	260	210	220	220

Example 8

Predicted Activities for Compounds of Formula IV

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula IV wherein R_6 and R_8 are hydrogen, and R_7 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 8 below. In this set of data the compound with the lowest predicted IC_{50}, 170 nM, had R_4 = dippip and Y_2 = diamine.

Table 8

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	1300	1200	1300	1300	510	1300	1300
	diamine	560	1200	1300	1200	640	1300	400
	dipamine	1100	1200	920	560	600	470	470
	dimor	180	1100	540	860	420	1100	470
	dipmor	690	830	460	380	310	300	500
	dipip	200	520	370	660	980	1100	390
	dippip	410	170	730	1200	500	1200	560

Example 9

Predicted Activities for Compounds of Formula IV

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula IV wherein R_6 and R_7 are hydrogen, and R_8 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 9 below. In this set of data the compound with the lowest predicted IC_{50}, 340 nM, had R_4 = dipmor and Y_2 = dimor.

Table 9

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	1300	1900	1900	1600	1600	1500	1600
	diamine	1200	1600	350	1500	1300	1400	380
	dipamine	810	560	1200	1300	1300	1200	1200
	dimor	1200	1500	1200	1300	1200	1200	1200
	dipmor	1200	1300	1500	340	1400	1300	1100

	dipip	1200	1500	1300	1300	1200	1200	610
	dippip	1100	1400	460	830	1200	780	1200

Example 10

Predicted Activities for Compounds of Formula IV

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula IV wherein R_7 is hydrogen, R_6 is Y_2, and R_8 is Y_3 (unsubsituted phenyl). Substitutions for R_4 and Y_2 were made as shown in Table 10 below. In this set of data the compound with the lowest predicted IC_{50}, 100 nM, had R_4 = dippip and Y_2 = pip.

Table 10

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	1200	1600	620	1300	730	1400	490
	diamine	730	480	990	1300	660	790	810
	dipamine	750	1200	380	310	1300	240	950
	dimor	1200	1200	1600	1200	1400	220	440
	dipmor	330	700	1600	1300	1300	1400	1000
	dipip	350	1200	880	1100	1100	320	330
	dippip	100	1300	120	1200	170	1200	460

Example 11

Predicted Activities for Compounds of Formula V

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula V wherein R_1, R_3, R_7, and R_8 are hydrogen, and R_6 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 11 below. In this set of data the compound with the lowest predicted IC_{50}, 38 nM, had R_4 = diamine and Y_2 = dippip.

Table 11

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	56	56	52	58	93	72	72

	diamine	42	42	58	50	45	42	38
	dipamine	73	83	63	79	65	82	62
	dimor	59	54	56	65	54	61	60
	dipmor	88	62	50	71	65	69	69
	dipip	43	40	65	65	60	52	56
	dippip	75	77	85	73	52	88	64

Example 12

Predicted Activities for Compounds of Formula V

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula V wherein R_1, R_3, R_6, and R_8 are hydrogen, and R_7 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 12 below. In this set of data the compound with the lowest predicted IC_{50}, 4.7 nM, had R_4 = pip and Y_2 = dipamine. Eleven additional compounds in this set of data had predicted IC_{50} values less than or equal to 30 nM.

Table 12

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	49	37	4.7	44	37	42	38
	diamine	57	30	38	35	19	35	34
	dipamine	87	29	5.6	28	29	39	65
	dimor	54	37	41	36	39	34	26
	dipmor	65	34	30	56	28	35	33
	dipip	49	43	16	31	33	9.2	36
	dippip	45	41	31	38	40	31	70

Example 13

Predicted Activities for Compounds of Formula V

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula V wherein R_1, R_3, R_6, and R_7 are hydrogen, and R_8 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 13 below. In this set of data the compound with the lowest predicted IC_{50}, 110 nM, had R_4 = dipamine and Y_2 = pip.

Table 13

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	2000	580	2000	310	1900	140	570
	diamine	160	750	970	1200	680	270	1100
	dipamine	110	240	270	230	600	330	240
	dimor	240	1000	670	370	880	1200	1300
	dipmor	140	450	590	250	510	360	470
	dipip	170	750	620	490	390	1100	400
	dippip	140	520	440	270	510	390	350

Example 14

Predicted Activities for Compounds of Formula V

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula V wherein R_1, R_6, R_7, and R_8 are hydrogen, and R_3 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 14 below. In this set of data two compounds shared the lowest predicted IC_{50}, 28 nM; one of these compounds had R_4 = dimor and Y_2 = dipamine, and the other compound had R_4 = dipip and Y_2 = dipamine.

Table 14

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	810	49	33	560	59	58	90
	diamine	340	74	130	470	36	80	220
	dipamine	850	160	130	230	1200	41	1200
	dimor	79	130	28	120	85	160	94
	dipmor	510	170	160	590	160	75	150
	dipip	350	53	28	100	330	590	100
	dippip	480	320	91	250	710	1500	330

Example 15

Predicted Activities for Compounds of Formula V

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula V wherein R_1, R_3, and R_7 are

hydrogen, R_6 is Y_2, and R_8 is Y_3 (unsubsituted phenyl). Substitutions for R_4 and Y_2 were made as shown in Table 15 below. In this set of data the compound with the lowest predicted IC_{50}, 2.4 nM, had R_4 = dippip and Y_2 = dipmor. Two additional compounds in this set of data had predicted IC_{50} values less than or equal to 30 nM.

Table 15

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	87	91	90	78	89	78	83
	diamine	210	110	360	750	1100	740	98
	dipamine	110	110	100	140	110	130	100
	dimor	270	740	940	800	900	210	1000
	dipmor	130	98	120	250	130	120	120
	dipip	330	310	400	640	580	230	500
	dippip	80	100	84	3.1	2.4	3.6	130

Example 16

Predicted Activities for Compounds of Formula V

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula V wherein R_1, R_6, and R_8 are hydrogen, R_3 is Y_3 (unsubsituted phenyl), and R_7 is Y_2. Substitutions for R_4 and Y_2 were made as shown in Table 16 below. In this set of data two compounds shared the lowest predicted IC_{50}, 27 nM; one of these compounds had R_4 = dippip and Y_2 = dipmor, and the other of these compounds had $R_4 = Y_2$ = dippip. One additional compound in this set of data had predicted IC_{50} value less than or equal to 30 nM.

Table 16

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	160	97	43	100	54	73	34
	diamine	320	62	50	200	48	76	39
	dipamine	210	70	73	170	96	240	63
	dimor	800	210	64	94	680	75	150
	dipmor	220	120	270	200	470	350	580
	dipip	530	120	54	210	38	200	63
	dippip	41	120	28	480	27	31	27

Example 17

Predicted Activities for Compounds of Formula V

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula V wherein R_3, R_6, and R_8 are hydrogen, R_1 is Y_3 (unsubsituted phenyl), and R_7 is Y_2. Substitutions for R_4 and Y_2 were made as shown in Table 17 below. In this set of data the compound with the lowest predicted IC_{50}, 31 nM, had R_4 = dippip and Y_2 = pip.

Table 17

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	310	150	100	250	210	270	110
	diamine	1200	1900	1400	2000	1900	1500	1900
	dipamine	490	320	250	400	590	1400	280
	dimor	400	2000	2000	2300	2100	2100	1300
	dipmor	790	440	190	660	540	960	180
	dipip	170	1500	1200	1400	1200	1600	140
	dippip	78	350	150	480	440	510	480

Example 18

Predicted Activities for Compounds of Formula V

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula V wherein R_3 and R_7 are hydrogen, R_6 is Y_2, and R_8 is Y_3 (unsubsituted phenyl). Substitutions for R_4 and Y_2 were made as shown in Table 18 below. In this set of data the compound with the lowest predicted IC_{50}, 28 nM, had R_4 = dimor and Y_2 = dipip.

Table 18

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	170	510	820	1800	640	1100	940
	diamine	120	120	150	160	120	130	150
	dipamine	810	200	150	740	170	130	480

	dimor	66	140	110	140	110	28	170
	dipmor	830	330	390	410	580	460	390
	dipip	100	110	110	180	200	130	130
	dippip	970	570	220	190	270	440	340

Example 19

Predicted Activities for Compounds of Formula VI

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula VI wherein R_3, R_7, and R_8 are hydrogen, and R_6 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 19 below. In this set of data two compounds shared the lowest predicted IC_{50}, 33 nM; one of these compounds had R_4 = dipip and Y_2 = dipmor, and the other compound had R_4 = Y_2 = dipip.

Table 19

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	110	76	53	61	64	38	64
	diamine	62	41	45	36	36	35	35
	dipamine	160	140	120	110	41	35	71
	dimor	73	37	34	37	36	35	36
	dipmor	150	38	40	71	75	50	59
	dipip	79	35	35	34	33	33	35
	dippip	75	40	43	55	38	94	37

Example 20

Predicted Activities for Compounds of Formula VI

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula VI wherein R_3, R_6, and R_8 are hydrogen, and R_7 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 20 below. In this set of data the compound with the lowest predicted IC_{50}, 60 nM, had R_4 = diamine and Y_2 = dippip.

Table 20

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	75	82	84	85	95	110	78
	diamine	81	110	78	74	91	80	60
	dipamine	89	120	120	86	120	83	79
	dimor	69	78	81	88	92	68	90
	dipmor	64	73	68	88	85	99	89
	dipip	78	74	74	66	70	92	81
	dippip	65	92	78	84	93	83	76

Example 21

Predicted Activities for Compounds of Formula VI

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula VI wherein R_3, R_6, and R_7 are hydrogen, and R_8 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 21 below. In this set of data the compound with the lowest predicted IC_{50}, 37 nM, had R_4 = dimor and Y_2 = diamine.

Table 21

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	630	110	320	260	370	290	170
	diamine	88	130	55	69	100	87	81
	dipamine	67	78	59	64	52	59	53
	dimor	81	37	53	79	82	62	84
	dipmor	140	51	60	79	59	85	70
	dipip	89	52	73	55	72	54	68
	dippip	73	54	52	52	63	60	61

Example 22

Predicted Activities for Compounds of Formula VI

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula VI wherein R_6, R_7, and R_8 are hydrogen, and R_3 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 22 below. In this set of data two compounds shared the lowest predicted IC_{50},

19 nM; one of these compounds had R_4 = dipip and Y_2 = dipamine, and the other compound had R_4 = dipip and Y_2 = dipamine. Three additional compounds in this set of data had predicted IC_{50} values less than or equal to 30 nM.

Table 22

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	50	23	27	36	39	55	43
	diamine	46	55	76	86	210	42	150
	dipamine	51	110	360	96	79	99	340
	dimor	42	57	95	43	97	74	120
	dipmor	80	54	100	320	80	82	150
	dipip	45	19	19	46	220	93	81
	dippip	54	87	230	27	4410	110	110

Example 23

Predicted Activities for Compounds of Formula VI

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula VI wherein R_1, R_6, and R_8 are hydrogen, R_3 is Y_3 (unsubsituted phenyl), and R_7 is Y_2. Substitutions for R_4 and Y_2 were made as shown in Table 23 below. In this set of data the compound with the lowest predicted IC_{50}, 41 nM, had R_4 = dipmor and Y_2 = dipip.

Table 23

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	510	57	49	270	80	66	88
	diamine	440	79	67	170	450	180	520
	dipamine	290	110	190	930	500	150	460
	dimor	300	120	74	69	200	69	640
	dipmor	190	150	71	780	320	41	330
	dipip	490	46	100	440	340	57	290
	dippip	290	52	69	110	1100	660	670

Example 24

Predicted Activities for Compounds of Formula VI

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula VI wherein R_1, R_6, and R_8 are hydrogen, R_3 is Y_3 (unsubsituted phenyl), and R_7 is Y_2. Substitutions for R_4 and Y_2 were made as shown in Table 24 below. In this set of data the compound with the lowest predicted IC_{50}, 31 nM, had R_4 = dippip and Y_2 = diamine.

Table 24

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	360	39	56	100	110	48	140
	diamine	530	160	87	150	94	64	78
	dipamine	540	60	150	180	910	96	330
	dimor	440	32	75	150	150	68	130
	dipmor	240	59	200	130	100	81	150
	dipip	340	51	77	140	37	36	88
	dippip	290	31	62	250	160	52	400

Example 25

Predicted Activities for Compounds of Formula VII

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula VII wherein R_1, R_3, R_7, and R_8 are hydrogen, and R_6 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 25 below. In this set of data the compound with the lowest predicted IC_{50}, 38 nM, had R_4 = dipamine and Y_2 = diamine.

Table 25

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	250	120	130	110	110	110	220
	diamine	79	60	270	130	120	290	69
	dipamine	160	38	240	170	650	400	580
	dimor	78	130	99	88	100	160	1300
	dipmor	350	250	670	150	250	57	100
	dipip	110	120	66	130	130	110	77
	dippip	150	190	150	140	120	100	130

Example 26

Predicted Activities for Compounds of Formula VII

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula VII wherein R_1, R_3, R_6, and R_8 are hydrogen, and R_7 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 26 below. In this set of data the compound with the lowest predicted IC_{50}, 22 nM, had R_4 = dimor and Y_2 = dippip.

Table 26

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	2100	110	120	91	110	100	110
	diamine	120	110	93	97	100	77	82
	dipamine	410	120	210	130	110	91	95
	dimor	98	94	90	74	98	120	22
	dipmor	170	88	110	110	120	35	120
	dipip	140	100	81	130	110	73	87
	dippip	100	99	110	76	120	190	120

Example 27

Predicted Activities for Compounds of Formula VII

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula VII wherein R_1, R_3, R_6, and R_7 are hydrogen, and R_8 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 27 below. In this set of data the compound with the lowest predicted IC_{50}, 130 nM, had R_4 = dipamine and Y_2 = dippip.

Table 27

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	1400	1200	1200	330	700	690	660
	diamine	510	1300	240	390	310	820	160
	dipamine	610	780	290	490	360	270	130

	dimor	680	1700	220	220	230	180	280
	dipmor	230	340	620	1300	230	280	710
	dipip	410	350	220	350	240	200	220
	dippip	410	320	820	630	210	420	180

Example 28

Predicted Activities for Compounds of Formula VII

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula VII wherein R_6, R_7, and R_8 are hydrogen, and R_3 is Y_1 (Ar-Y_2). Substitutions for R_4 and Y_2 were made as shown in Table 28 below. In this set of data the compound with the lowest predicted IC_{50}, 18 nM, had R_4 = Y_2 = dimor. Three additional compounds in this set of data had predicted IC_{50} values less than or equal to 30 nM.

Table 28

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	43	59	87	90	130	96	40
	diamine	42	62	120	65	42	35	250
	dipamine	71	93	140	140	75	130	110
	dimor	36	37	120	18	280	190	85
	dipmor	75	49	30	110	170	440	70
	dipip	40	38	89	48	88	38	170
	dippip	58	24	26	200	230	88	170

Example 29

Predicted Activities for Compounds of Formula VII

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula VII wherein R_1, R_3, and R_7 are hydrogen, R_6 is Y_2, and R_8 is Y_3 (unsubsituted phenyl). Substitutions for R_4 and Y_2 were made as shown in Table 29 below. In this set of data the compound with the lowest predicted IC_{50}, 95 nM, had R_4 = dipamine and Y_2 = dipip.

Table 29

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	2000	1900	1100	1200	840	730	790
	diamine	220	250	1000	300	210	280	390
	dipamine	1500	210	920	1800	1600	95	610
	dimor	400	180	900	320	370	240	780
	dipmor	1600	1700	730	1000	1200	1400	580
	dipip	470	290	250	520	380	170	210
	dippip	200	440	1300	1700	920	1000	820

Example 30

Predicted Activities for Compounds of Formula X

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula X wherein R_3, R_6, R_7, and R_8 are hydrogen, and Y_1 is Ar-Y_2. Substitutions for R_4 and Y_2 were made as shown in Table 30 below. In this set of data the compound with the lowest predicted IC_{50}, 29 nM, had R_4 = pip and Y_2 = dippip.

Table 30

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	66	39	48	33	42	65	29
	diamine	64	78	58	36	58	95	180
	dipamine	220	160	48	120	96	43	170
	dimor	120	110	44	120	62	54	45
	dipmor	180	53	340	46	350	190	54
	dipip	110	100	100	61	32	67	72
	dippip	51	170	160	110	80	66	190

Example 31

Predicted Activities for Compounds of Formula XI

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XI wherein R_3, R_6, R_7, and R_8 are hydrogen, and Y_1 is Ar-Y_2. Substitutions for R_4 and Y_2 were made as shown in Table 31 below. In this set of data the compound with the lowest predicted IC_{50}, 0.82 nM,

had R_4 = dipip and Y_2 = dimor. Forty-two additional compounds in this set of data had predicted IC_{50} values less than or equal to 30 nM.

Table 31

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	4.6	1.7	6.6	3.2	2.4	2.8	4.5
	diamine	18	2.8	4.5	0.89	1.8	2.7	25
	dipamine	8.8	3.1	4.6	1.5	2.1	2.6	27
	dimor	34	3.1	1.6	1.1	34	1.9	4.3
	dipmor	35	1.5	29	2.5	32	2.7	1.9
	dipip	47	11	1.5	0.82	1.6	2.3	7.3
	dippip	90	1.1	2.9	1.1	9.5	14	12

Example 32

Predicted Activities for Compounds of Formula XIV

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XIV wherein R_3, R_7, and R_8 are hydrogen and R_6 is Y_3. Substitutions for R_4 and Y_2 were made as shown in Table 32 below. In this set of data the compound with the lowest predicted IC_{50}, 49 nM, had R_4 = dippip and Y_2 = dipip. One additional compound in this set of data had a predicted IC_{50} value less than or equal to 30 nM.

Table 32

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	86	51	53	48	53	51	55
	diamine	350	150	230	1100	88	110	360
	dipamine	100	36	140	93	98	38	170
	dimor	570	170	130	490	160	260	97
	dipmor	94	35	260	110	470	170	120
	dipip	160	240	93	280	200	120	290
	dippip	140	6.8	66	190	70	2	35

Example 33

Predicted Activities for Compounds of Formula XIV

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XIV wherein R_3, R_6, and R_7 are hydrogen and R_8 is Y_3. Substitutions for R_4 and Y_2 were made as shown in Table 33 below. In this set of data the compound with the lowest predicted IC_{50}, 44 nM, had R_4 = dimor and Y_2 = pip.

Table 33

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	260	300	110	180	100	600	150
	diamine	280	680	330	89	320	150	46
	dipamine	46	1000	580	200	390	230	93
	dimor	44	1400	120	1300	160	970	390
	dipmor	580	460	1100	810	620	1000	310
	dipip	370	220	120	310	130	56	190
	dippip	72	95	740	1100	950	63	160

Example 34

Predicted Activities for Compounds of Formula XV

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XV wherein R_7 and R_8 are hydrogen and R_6 is Y_3. Substitutions for R_4 and Y_2 were made as shown in Table 34 below. In this set of data the compound with the lowest predicted IC_{50}, 39 nM, had R_4 = dipmor and Y_2 = diamine.

Table 34

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	89	43	71	40	46	39	54
	diamine	200	1500	54	1300	140	1300	550
	dipamine	79	40	62	85	130	66	370
	dimor	190	1200	110	1200	53	740	250
	dipmor	85	39	71	42	150	240	95
	dipip	190	330	150	1400	370	150	69
	dippip	88	49	95	54	52	49	42

Example 35

Predicted Activities for Compounds of Formula XV

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XV wherein R_6 and R_7 are hydrogen and R_8 is Y_3. Substitutions for R_4 and Y_2 were made as shown in Table 35 below. In this set of data the compound with the lowest predicted IC_{50}, 49 nM, had R_4 = dipamine and Y_2 = dipip.

Table 35

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	240	780	120	570	120	520	150
	diamine	230	290	150	1100	140	500	110
	dipamine	510	250	370	500	730	49	710
	dimor	58	1400	230	520	230	1400	590
	dipmor	750	1000	740	520	1200	1500	870
	dipip	410	1300	110	57	130	1200	550
	dippip	650	160	480	1300	400	1400	1200

Example 36

Predicted Activities for Compounds of Formula XVI

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XVI wherein R_3, R_7, and R_8 are hydrogen and R_6 is Y_3. Substitutions for R_4 and Y_2 were made as shown in Table 36 below. In this set of data the compound with the lowest predicted IC_{50}, 62 nM, had R_4 = dippip and Y_2 = dipamine.

Table 36

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	97	210	110	1400	500	280	220
	diamine	290	75	84	170	520	73	240
	dipamine	310	240	110	210	140	110	280

	dimor	230	74	100	170	290	87	73
	dipmor	130	200	93	170	400	77	170
	dipip	120	180	79	160	300	270	240
	dippip	140	140	62	200	240	80	250

Example 37

Predicted Activities for Compounds of Formula XVI

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XVI wherein R_3, R_6, and R_7 are hydrogen and R_8 is Y_3. Substitutions for R_4 and Y_2 were made as shown in Table 37 below. In this set of data the compound with the lowest predicted IC_{50}, 50 nM, had R_4 = diamine and Y_2 = dipip.

Table 37

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	480	440	1400	1300	1200	380	1200
	diamine	210	270	600	350	720	50	870
	dipamine	340	710	400	130	310	350	740
	dimor	1200	820	1400	1000	1300	340	1100
	dipmor	1500	420	1200	590	1500	880	1300
	dipip	220	550	970	860	1500	1200	1200
	dippip	150	390	120	170	1500	96	1300

Example 38

Predicted Activities for Compounds of Formula XVII

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XVII wherein R_3, R_7, and R_8 are hydrogen and R_6 is Y_3. Substitutions for R_4 and Y_2 were made as shown in Table 38 below. In this set of data the compound with the lowest predicted IC_{50}, 22 nM, had R_4 = dippip and Y_2 = dipip.

Table 38

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	44	39	59	39	80	38	110
	diamine	81	160	94	170	180	240	120
	dipamine	81	160	130	53	56	99	180
	dimor	89	240	310	300	200	310	160
	dipmor	75	31	61	61	280	85	270
	dipip	170	240	120	500	240	200	230
	dippip	60	41	72	55	35	22	31

Example 39

Predicted Activities for Compounds of Formula XX

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XX wherein R_3, R_7, and R_8 are hydrogen and R_6 is Y_2. Substitutions for R_4 and Y_2 were made as shown in Table 39 below. In this set of data the compound with the lowest predicted IC_{50}, 16 nM, had R_4 = dippip and Y_2 = pip. Five additional compounds in this set of data had predicted IC_{50} values less than or equal to 30 nM.

Table 39

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	42	31	30	32	57	35	55
	diamine	40	57	130	50	62	80	100
	dipamine	14	56	72	30	190	41	180
	dimor	17	42	140	64	100	85	79
	dipmor	47	44	130	32	110	73	110
	dipip	17	42	77	72	87	68	100
	dippip	16	55	140	66	53	96	130

Example 40

Predicted Activities for Compounds of Formula XXI

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XXI wherein R_7 and R_8 are hydrogen and R_6 is Y_2. Substitutions for R_4 and Y_2 were made as shown in Table 40

below. In this set of data the compound with the lowest predicted IC_{50}, 9.4 nM, had R_4 = dipmor and Y_2 = pip. Five additional compounds in this set of data had predicted IC_{50} values less than or equal to 30 nM.

Table 40

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	55	35	61	33	48	42	71
	diamine	25	62	49	39	98	68	42
	dipamine	15	70	62	61	53	63	51
	dimor	18	55	120	64	100	69	120
	dipmor	9.4	58	63	63	150	54	75
	dipip	24	44	120	72	110	32	110
	dippip	17	71	54	57	83	67	150

Example 41

Predicted Activities for Compounds of Formula XXI

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XXI wherein R_6 and R_8 are hydrogen and R_7 is Y_2. Substitutions for R_4 and Y_2 were made as shown in Table 41 below. In this set of data the compound with the lowest predicted IC_{50}, 8.7 nM, had R_4 = dippip and Y_2 = pip. Two additional compounds in this set of data had predicted IC_{50} values less than or equal to 30 nM.

Table 41

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	360	71	87	83	80	77	69
	diamine	68	60	59	45	53	39	65
	dipamine	40	40	180	67	89	48	120
	dimor	78	62	84	50	76	50	64
	dipmor	12	29	73	57	60	32	66
	dipip	43	34	69	62	56	61	76
	dippip	8.7	56	47	55	73	70	72

Example 42

Predicted Activities for Compounds of Formula XXII

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XXII wherein R_3, R_7, and R_8 are hydrogen and R_6 is Y_2. Substitutions for R_4 and Y_2 were made as shown in Table 42 below. In this set of data the compound with the lowest predicted IC_{50}, 36 nM, had R_4 = dipip and Y_2 = pip.

Table 42

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	46	61	75	4	620	50	120
	diamine	41	62	57	120	170	250	63
	dipamine	55	84	280	300	1300	190	1500
	dimor	53	80	330	53	59	92	81
	dipmor	49	130	86	780	1000	360	1100
	dipip	36	80	56	850	100	170	240
	dippip	44	61	180	100	610	120	440

Example 43

Predicted Activities for Compounds of Formula XXII

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XXII wherein R_3, R_6, and R_8 are hydrogen and R_7 is Y_2. Substitutions for R_4 and Y_2 were made as shown in Table 43 below. In this set of data the compound with the lowest predicted IC_{50}, 26 nM, had R_4 = dimor and Y_2 = dipmor. Two additional compounds in this set of data had predicted IC_{50} values less than or equal to 30 nM.

Table 43

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	280	540	230	1200	1200	1200	1600
	diamine	78	42	48	130	720	86	77
	dipamine	57	40	110	200	140	69	58
	dimor	91	61	150	220	26	74	770
	dipmor	59	48	64	470	730	76	730

	dipip	110	41	40	76	280	71	76
	dippip	39	180	240	930	290	76	190

Example 44

Predicted Activities for Compounds of Formula XXIII

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XXIII wherein R_3, R_7, and R_8 are hydrogen and R_6 is Y_2. Substitutions for R_4 and Y_2 were made as shown in Table 44 below. In this set of data the compound with the lowest predicted IC_{50}, 9.7 nM, had R_4 = dippip and Y_2 = pip. Five additional compounds in this set of data had predicted IC_{50} values less than or equal to 30 nM.

Table 44

		Y_2						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_4	**pip**	98	54	75	45	68	56	67
	diamine	36	55	57	42	68	61	200
	dipamine	16	69	110	55	260	87	250
	dimor	25	52	49	72	48	70	99
	dipmor	16	51	83	74	99	73	22
	dipip	23	37	76	100	94	45	94
	dippip	9.7	72	73	120	110	50	110

Example 45

Predicted Activities for Compounds of Formula XXX

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XXX wherein each of R_3, R_{15}, R_5, R_6, R_7, and R_8 is hydrogen, and each of Q_p and Q_o is Y_2. Substitutions for Q_p and Q_o were made as shown in Table 45 below. In this set of data the compound with the lowest predicted IC_{50}, 2.9 nM, had Q_p = dipip and Q_o = pip. Eighteen additional compounds in this set of data had predicted IC_{50} values less than or equal to 30 nM.

Table 45

		Q_p						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
Q_o	**pip**	26	17	5.3	8.3	4.6	2.9	14
	diamine	26	45	41	33	50	19	42
	dipamine	31	24	40	40	44	52	52
	dimor	608	5.3	22	13	23	38	40
	dipmor	30	36	67	53	45	42	49
	dipip	34	36	6.9	45	43	6.5	42
	dippip	38	6	55	52	84	13	5.9

Example 46

Predicted Activities for Compounds of Formula XXXI

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XXXI wherein each of R_3, R_{15}, R_5, R_7, and R_8 is hydrogen; and each of R_6 and Q is Y_2. Substitutions for R_6 and Q were made as shown in Table 46 below. In this set of data two compounds shared the lowest predicted IC_{50}, 32 nM; one of these compounds had Q = dipmor and R_6 = dippip, and the other had Q = dipip and R_6 = diamine.

Table 46

		Q						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_6	**pip**	67	41	50	43	50	40	72
	diamine	67	48	41	49	38	32	38
	dipamine	73	35	47	49	60	38	38
	dimor	57	38	55	39	46	35	38
	dipmor	68	37	60	46	44	36	40
	dipip	59	34	45	46	50	35	45
	dippip	57	35	36	44	32	36	33

Example 47

Predicted Activities for Compounds of Formula XXXII

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XXXII wherein each of R_{15}, R_5, R_6, R_7, and R_8 is hydrogen, and each of Q_p and Q_o is Y_2. Substitutions for Q_p and Q_o

were made as shown in Table 47 below. In this set of data two compounds shared the lowest predicted IC_{50}, 1.5 nM; one of these compounds had Q_p = dipamine and Q_o = pip, and the other compound had Q_1 = dipip and Q_2 = pip. Thirty-four additional compounds in this set of data had predicted IC_{50} values less than or equal to 30 nM.

Table 47

		Q_p						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
Q_o	**pip**	13	8.8	1.5	5.9	2.3	1.5	4.5
	diamine	2	8.8	1.9	40	43	18	45
	dipamine	38	35	9.5	48	51	17	57
	dimor	11	2.9	25	26	2.3	6.2	40
	dipmor	17	9.3	11	46	13	17	53
	dipip	13	7.9	4.3	7.9	13	48	2.7
	dippip	14	16	13	16	66	12	18

Example 48

Predicted Activities for Compounds of Formula XXXIII

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XXXIII wherein each of R_{15}, R_5, R_7, and R_8 is hydrogen; and each of R_6 and Q is Y_2. Substitutions for R_6 and Q were made as shown in Table 48 below. In this set of data the compound with the lowest predicted IC_{50}, 33 nM, had Q = R_6 =dippip.

Table 48

		Q						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_6	**pip**	83	70	57	53	62	53	160
	diamine	56	35	75	40	46	41	49
	dipamine	65	40	46	45	37	49	44
	dimor	59	47	52	53	50	44	43
	dipmor	64	51	56	48	45	40	40
	dipip	60	41	59	44	46	36	45
	dippip	61	49	54	47	53	40	33

Example 49

Predicted Activities for Compounds of Formula XXXIV

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XXXIV wherein each of R_1, R_3, R_{15}, R_6, R_7, and R_8 is hydrogen, and each of Q_p and Q_o is Y_2. Substitutions for Q_p and Q_o were made as shown in Table 49 below. In this set of data the compound with the lowest predicted IC_{50}, 26 nM, had $Q_p = Q_o$ = pip.

Table 49

		Q_p						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
Q_o	**pip**	26	40	180	86	480	63	55
	diamine	240	82	110	1200	180	75	40
	dipamine	100	35	300	1100	340	77	330
	dimor	43	57	490	1200	1200	100	48
	dipmor	61	33	150	210	1200	1200	1100
	dipip	42	51	54	80	33	93	740
	dippip	54	140	180	1400	120	140	340

Example 50

Predicted Activities for Compounds of Formula XXXV

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XXXV wherein each of R_3, R_{15}, R_7, and R_8 is hydrogen; and each of R_6 and Q is Y_2. Substitutions for R_6 and Q were made as shown in Table 50 below. In this set of data the compound with the lowest predicted IC_{50}, 31 nM, had Q = dimor and R_6 =dippip.

Table 50

		Q						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
R_6	**pip**	1200	1200	400	530	220	470	150
	diamine	1200	1200	500	1200	1200	1100	1300
	dipamine	1300	420	620	1100	1300	720	310
	dimor	1200	1200	250	1200	250	1200	700
	dipmor	1200	460	590	460	470	1200	200
	dipip	1300	1200	1300	1200	430	1100	430

	dippip	38	330	35	31	36	38	34

Example 51

Predicted Activities for Compounds of Formula XXXVI

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XXXVI wherein each of R_3, R_{15}, R_6, R_7, and R_8 is hydrogen, and each of Q_p and Q_o is Y_2. Substitutions for Q_p and Q_o were made as shown in Table 51 below. In this set of data the compound with the lowest predicted IC_{50}, 1.5 nM, had Q_p = dipamine and Q_o = pip. Thirty-five additional compounds in this set of data had predicted IC_{50} values less than or equal to 30 nM.

Table 51

		Q_p						
		pip	**diamine**	**dipamine**	**dimor**	**dipmor**	**dipip**	**dippip**
Q_o	**pip**	16	9.1	1.5	6.6	8.6	34	2.9
	diamine	25	18	27	4.5	11	26	34
	dipamine	40	9.7	22	6.3	33	39	33
	dimor	22	12	2.9	32	27	31	32
	dipmor	48	8.4	15	18	44	30	28
	dipip	18	5.4	7.3	30	22	26	15
	dippip	33	28	4	28	29	28	33

Example 52

Predicted Activities for Compounds of Formula XXXVII

Based on computer modeling, IC_{50} values (nM) were predicted in respect of TLR9 activity for compounds according to Formula XXXVII wherein each of R_3, R_{15}, R_7, and R_8 is hydrogen; and each of R_6 and Q is Y_2. Substitutions for R_6 and Q were made as shown in Table 52 below. In this set of data the compound with the lowest predicted IC_{50}, 26 nM, had Q = dimor and R_6 =dippip. Seventeen additional compounds in this set of data had predicted IC_{50} values less than or equal to 30 nM.

Table 52

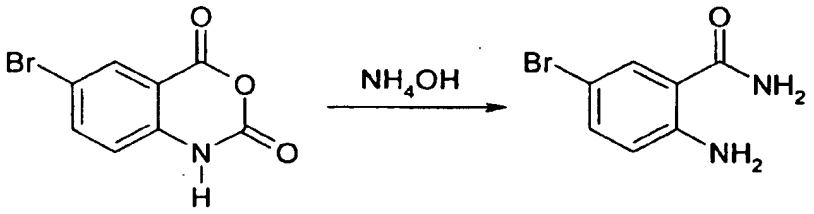
		Q						
		pip	diamine	dipamine	dimor	dipmor	dipip	dippip
R_6	pip	72	29	39	28	31	28	39
	diamine	65	32	35	27	36	28	34
	dipamine	58	33	31	27	64	30	31
	dimor	36	28	37	27	34	31	38
	dipmor	38	28	31	27	35	27	35
	dipip	36	28	38	27	43	27	43
	dippip	55	30	33	26	35	27	33

Example 53

Synthesis of Compound #401-92

Step 1

Preparation of 5-bromoanthranilamide

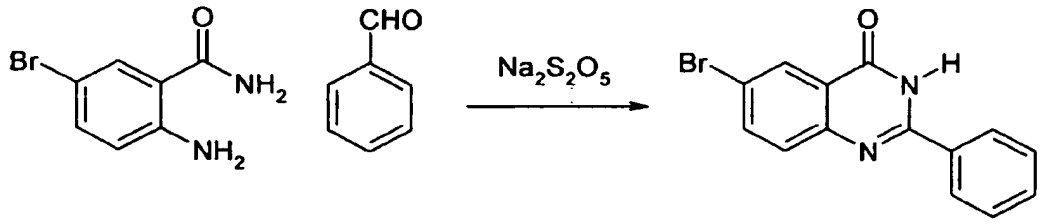


242.03 215.05

To a stirred slurry of 5-bromoisatoic anhydride (10 gm, 4.13 X 10^{-2} moles; Aldrich Chemical, product number 477702) in dry tetrahydrofuran (THF; 50 mL) was added concentrated ammonium hydroxide solution (20 mL). The anhydride quickly dissolved forming a clear solution. After about 2 minutes a biphasic mixture had formed. This was stirred for 1 hour and was then kept at room temperature overnight. The THF was evaporated under vacuum to give a thick slurry. Water (20 mL) was added and the solid product was isolated by filtration. The anthranilamide was washed with water and dried at 80 °C to provide 6.3 gm (70.9%) of the product as a white solid. Thin layer chromatography (TLC; silica, 10% methanol in methylene chloride) showed only the product spot.

Step 2

Preparation of 6-bromo-2-phenylquinazolin-4-one

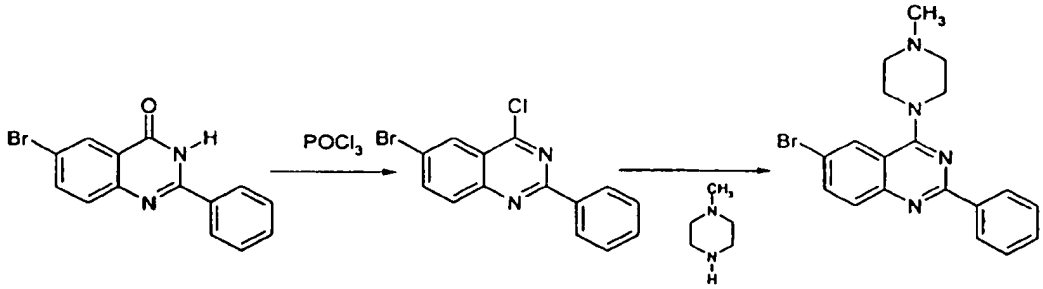


215.05 106.12 301.14

A mixture of 5-bromoanthranilamide (7.5 gm, 3.49 X 10^{-2} moles), benzaldehyde (3.7 gm, 3.49 X 10^{-2} moles), sodium metabisulfite (4.98 gm, 2.62 X 10^{-2} moles), and water (0.5 mL) in dimethylacetamide (50 mL) was stirred at 150 °C for 2 hours. The slurry was cooled to 50 °C and water (200 mL) was added. This slurry was stirred for 10 minutes and was then filtered to isolate the product. The solid was washed well on the filter with water. While still damp, the solid product was recrystallized from dimethylformamide to give the quinazolinone as an off white solid in a yield of 4.45 gm (42.3%).

Step 3

Preparation of 6-bromo-4-(4-methyl-1-piperazinyl)-2-phenylquinazoline



301.14 319.59 383.29

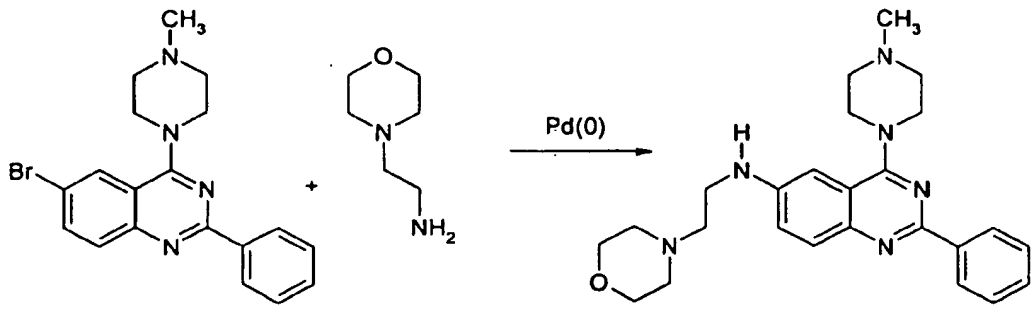
A slurry of 6-bromo-2-phenylquinazolin-4-one (4.44 gm, 1.47 X 10^{-2} moles) was stirred and heated in 1,2-dichlorobenzene (40 mL) to 130 °C. Phosphorus oxychloride (4.52 gm, 2.95 X 10^{-2} moles) was added to the stirred, hot mixture over a 5 minute period. The mixture was stirred at 130 °C until a clear orange solution

formed and then for an additional 30 minutes. The total reaction time was 2 hours. After cooling to room temperature the reaction solution was diluted with *tert*-butylmethyl ether (200 mL) and the solution was shaken in a separatory funnel with water (200 mL). The aqueous phase (pH = 2.0) was discarded and the organic solution was washed with a solution of sodium hydroxide (5.88 gm, 0.147 moles) in water (200 mL). The *tert*-butylmethyl ether was stripped under vacuum to give a slurry of 6-bromo-4-chloro-2-phenylquinazoline in 1,2-dichlorobenzene.

This slurry was diluted with n-butanol (40 mL) and N-methylpiperazine (4.4 gm, 4.4 X 10^{-2} moles) was added. This mixture was heated to reflux which caused the formation of a clear yellow solution. The solution was kept at reflux for 30 minutes at which point TLC (silica, 10% methanol in methylene chloride) showed that all of the starting material had been consumed with the formation of a single product. The solution was cooled to room temperature and was diluted with *tert*-butylmethyl ether (200 mL). This solution was extracted once with 10% hydrochloric acid (150 mL). These acidic extracts were stirred and made basic by the addition of 10% sodium hydroxide. The precipitated product was extracted into methylene chloride (200 mL). Methylene chloride was evaporated under vacuum to provide the product as an oil in a crude yield of 5.2 gm (92%). The oil was dissolved in hexane (25 mL) and with scratching, the product crystallized. The solid was isolated by filtration, washed with hexane and dried to give 2.5 gm (44.4%) of purified 6-bromo-4-(4-methyl-1-piperazinyl)-2-phenylquinazoline as an off white solid.

Step 4

Preparation of 6-N-[2-(4-morpholinyl)ethyl]-4-[4-methyl-1-piperazinyl]-2-phenylquinazoline



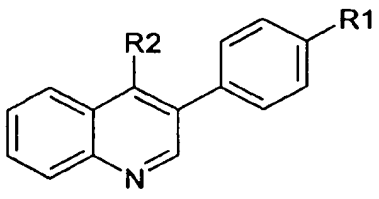
383.29	130.19	432.57
		#401-92

A mixture of 6-bromo-4-(4-methyl-1-piperazinyl)-2-phenylquinazoline (1.0 gm, 2.6 X 10^{-3} moles), tris-dibenzylideneacetone dipalladium(0) (23.8 mg, 2.6 X 10^{-5} moles), racemic 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (+/- Binap; 48.6 mg, 7.8 X 10^{-5} moles), sodium *t*-butoxide (350 mg, 3.6 X 10^{-3} moles) and toluene (5 mL) was stirred as argon was passed through. The flask was sealed with a septum and 2-morpholinoethylamine (406 mg, 3.12 X 10^{-3} moles) dissolved in toluene was added by syringe. The reaction mixture was stirred at 90 °C for 2 hours. TLC of an aliquot (silica, 10% methanol in methylene chloride) showed complete conversion of the starting quinazoline to a single new product. The mixture was cooled and diluted with ethyl acetate (100 mL). This was washed with water (100 mL) and then extracted with 10% hydrochloric acid (2 X 25 mL). The combined extracts were washed once with ethyl acetate (25 mL) and were then made basic by the addition of 10% sodium hydroxide solution. The product that separated from the basified mixture was extracted into methylene chloride (2 X 25 mL). The combined extracts were evaporated to give 6-N-[2-(4-morpholinyl)ethyl]-4-[4-methyl-1-piperazinyl]-2-phenylquinazoline as a pale yellow solid in a yield of 1.02 gm (90.7%).

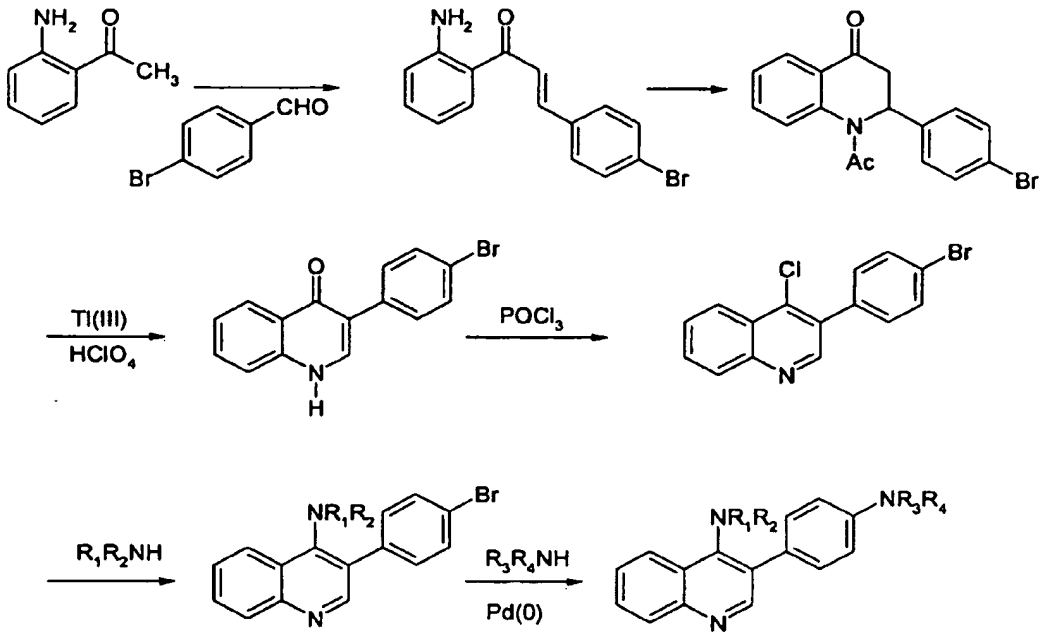
Example 54

Synthesis of Compounds of Formula III

Compounds of class A3I represent compounds of Formula III wherein R_6, R_7, and R_8 are hydrogen and R_3 is Y_1 (Ar-Y_2), as defined herein.



A3I

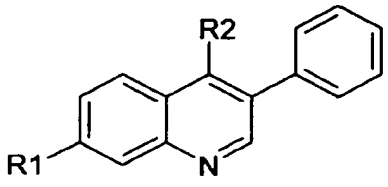


Compounds of the A3I class are synthesized in the following manner. 2-Aminoacetophenone and 4-bromobenzaldehyde are condensed in the presence of alkali to provide 2-amino-4'-bromochalcone. The chalcone is cyclized to the dihydroquinolone in the presence of phosphoric acid and subsequently acetylated with acetic anhydride as described by Donnelley and Farrell. Donnelly JA et al. (1990) *J Org Chem* 55:1757-61. This dihydroquinolone is oxidized and rearranged in the presence of thallium salts and perchloric acid to the 3-aryl-4-quinolone as described by Singh and Kapil. Singh OV et al. (1992) *SYNLETT* 751-2. Conversion to the 4-chloroquinoline is achieved by the usual method using phosphorus oxychloride. Displacement of the chlorine in the 4 position of the quinoline with a primary or secondary alkyl amine provides the 3-(4-bromophenyl)-4-alkylaminoquinoline which is converted to the A3I using the Buchwald amination procedure. Buchwald SL et al. (2004) *Org Syn* Coll. Vol. 10:423.

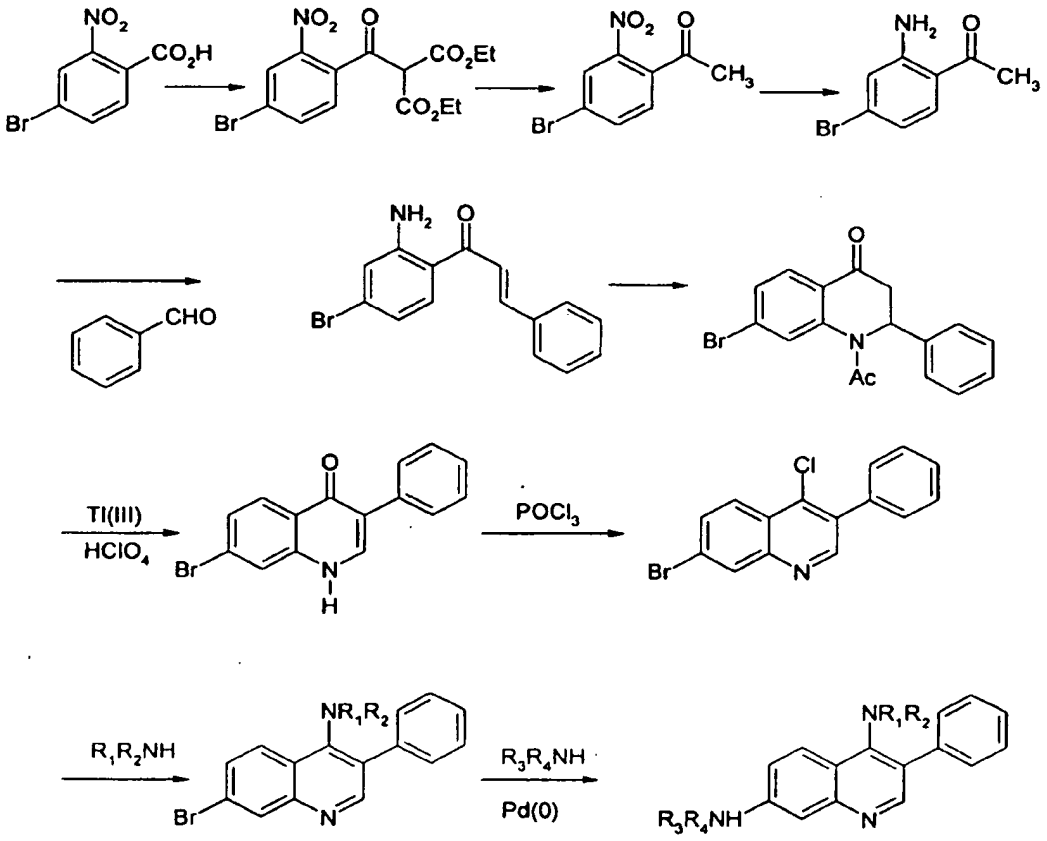
Example 55

Synthesis of Compounds of Formula III

Compounds of class AbI represent compounds of Formula III wherein R_6 and R_8 are hydrogen, R_3 is Y_3 (unsubstituted phenyl), and R_7 is Y_2, as defined herein.



AbI



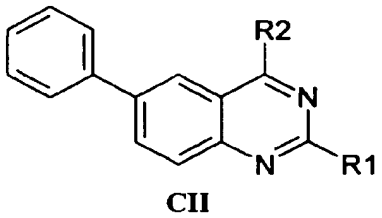
Compounds of the form AbI are synthesized using the methods described in the synthesis of compounds of form A3I (Example 54). In the case of the AbI compounds, the starting 2-amino-4-bromo is prepared from the commercially available 2-nitro-4-bromobenzoic acid by acylation of diethylmalonate followed by hydrolysis and decarboxylation to 2-nitro-4-bromoacetophenone (Reynolds GA et al. (1963) *Org Syn* Coll. Vol. 4:708) and subsequent reduction to 2-amino-4-

bromoacetophenone. In the case of the Abl compounds the bromine on the quinoline ring is displaced with an amine using Buchwald amination as described earlier.

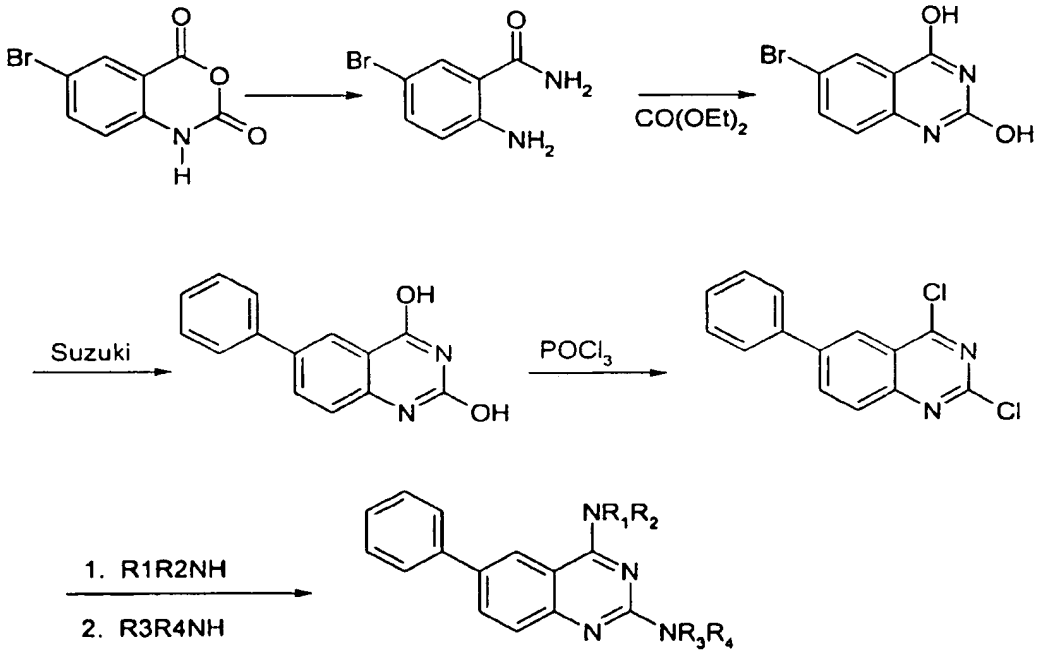
Example 56

Synthesis of Compounds of Formula XV

Compounds of class CII represent compounds of Formula XV wherein R_7 and R_8 are hydrogen and R_6 is Y_3, as defined herein.



CII



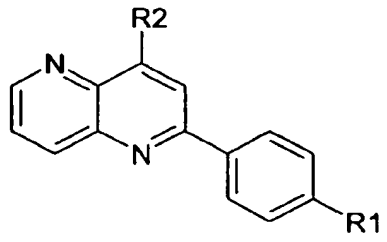
CII compounds are made by conversion of 5-bromoisatoic anhydride to 5-bromoanthranilamide in the presence of ammonium hydroxide. Condensation with diethyl malonate provides the 2,4-dihydroxy-6-bromoquinazoline. Suzuki coupling

(Goodson FE et.al. (2004) *Org Syn* Coll. Vol. 10:501) is used to synthesize 2,4-dihydroxy-6-phenylquinazoline which is converted to the dichloroquinazoline through the use of phosphorus oxychloride. Sequential displacement of the chlorine in the 4-position of the quinazoline followed by displacement of the chlorine in the 2-position by the same or different amines provides the CII compounds.

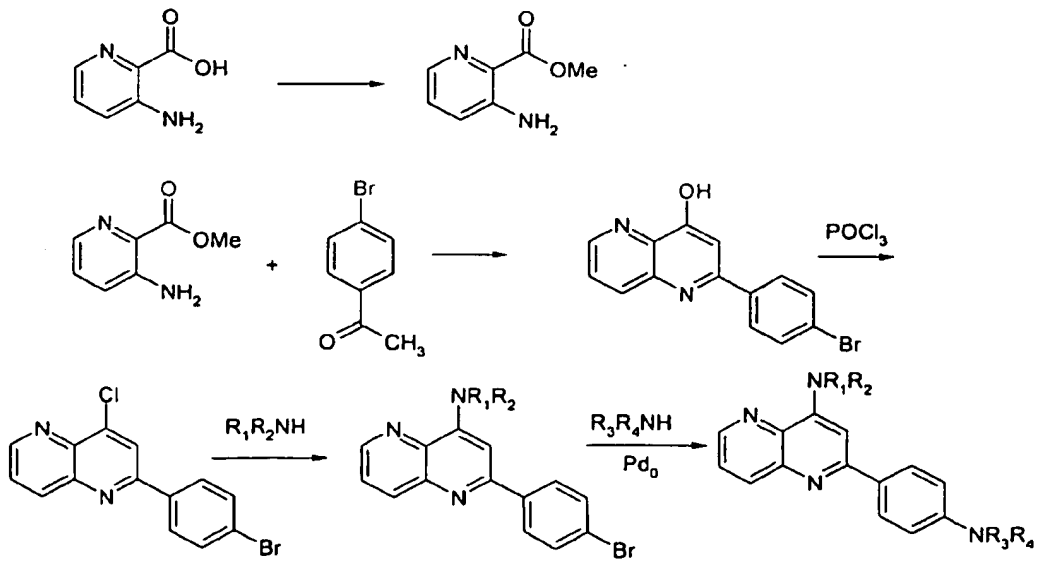
Example 57

Synthesis of Compounds of Formula XI

Compounds of class BIV represent compounds of Formula XI wherein R_3, R_6, R_7, and R_8 are hydrogen and Y_1 is Ar-Y_2, as defined herein.



BIV

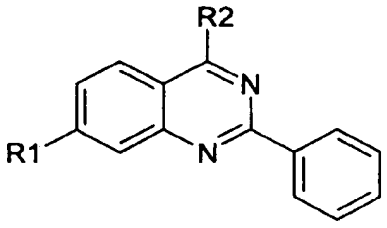


BIV compounds are prepared by condensation of 3-aminopicolinic acid , via its methyl ester, with 4-bromoacetophenone to give 2-(4-bromophenyl)-4-hydroxynaphthyridine. Conversion to the 4-chloro naphthyridine and displacement of the chlorine first, followed by the bromine are achieved by methods described above.

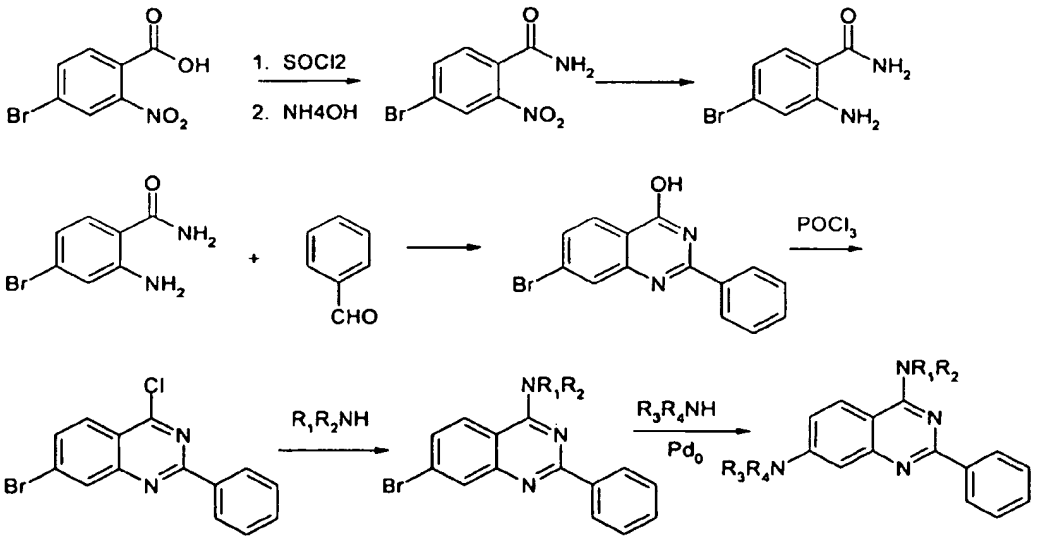
Example 58

Synthesis of Compounds of Formula XXI

Compounds of class DbII represent compounds of Formula XXI wherein R_6 and R_8 are hydrogen and R_7 is Y_2, as defined herein.



DbII



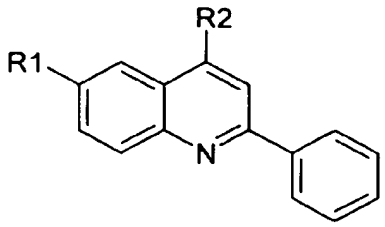
The starting point for the synthesis of the DbII compounds is 2-nitro-4-bromobenzoic acid. This is converted to 4-bromoanthranilamide by forming the acid chloride and aminating this with ammonium hydroxide. Condensation with

benzaldehyde in the presence of sodium bisulfite (Imai Y et al. (1981) *Synthesis* 1:35) gives 2-phenyl-4-hydroxy-7-bromoquinazoline. Formation of the DbII compounds involves the conversion of the 4-hydroxyquinazoline to the 4-chloroquinazoline followed by displacement of the chlorine and then the bromine with amines by the methods described earlier.

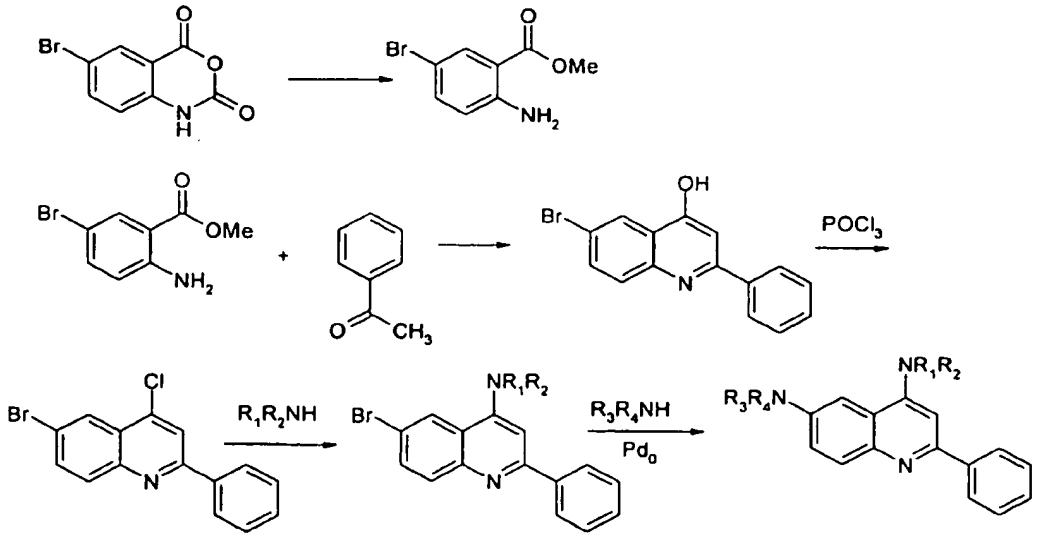
Example 59

Synthesis of Compounds of Formula XX

Compounds of class DI represent compounds of Formula XX wherein R_3, R_7, and R_8 are hydrogen and R_6 is Y_2, as defined herein.



DI



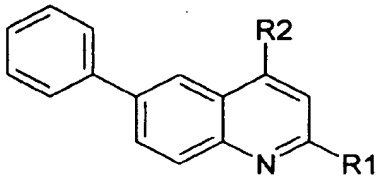
The synthesis of DI compounds starts with 5-bromoisatoic anhydride. This is converted to methyl-5-bromoanthranilate by reaction with methanol. Condensation

with acetophenone provides 2-phenyl-4-hydroxy-6-bromoquinoline. This is converted to the 4-chloroquinoline by reaction with phosphorus oxychloride. Displacement of the chlorine and then the bromine with amines by the methods described earlier provide the DI compounds

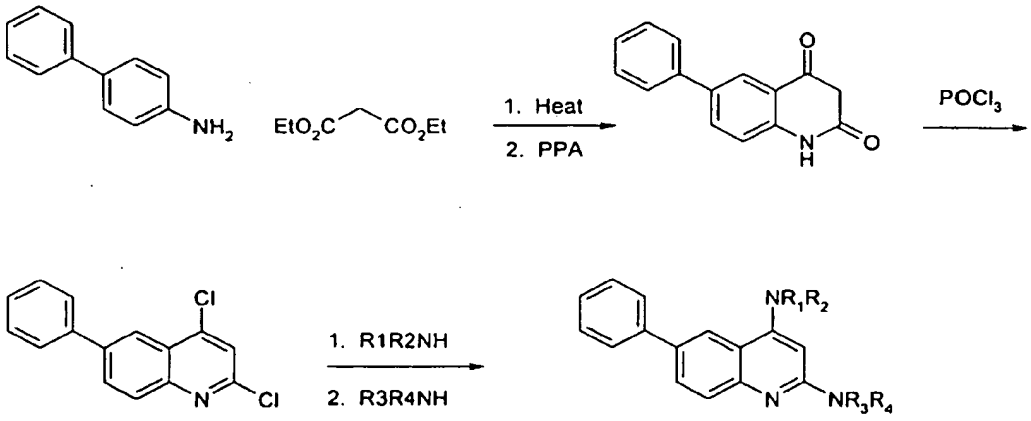
Example 60

Synthesis of Compounds of Formula XIV

Compounds of class CI represent compounds of Formula XIV wherein R_3, R_7, and R_8 are hydrogen and R_6 is Y_3, as defined herein.



CI



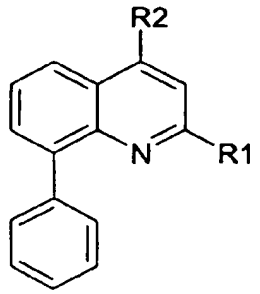
Condensation of 4-aminobiphenyl with diethyl malonate in polyphosphoric acid is used to synthesize 2,4-dihydroxy-6-phenylquinoline. This is converted to the 2,4-dichloro-6-phenylquinoline by reaction with phosphorus oxychloride. Sequential displacement of the chlorine in the 2-position of the quinoline followed by displacement of the chlorine in the 4-position by the same or different amines (Lister

T et al (2003) *Australian Journal of Chemistry* 56(9):913-6) provides the CI compounds.

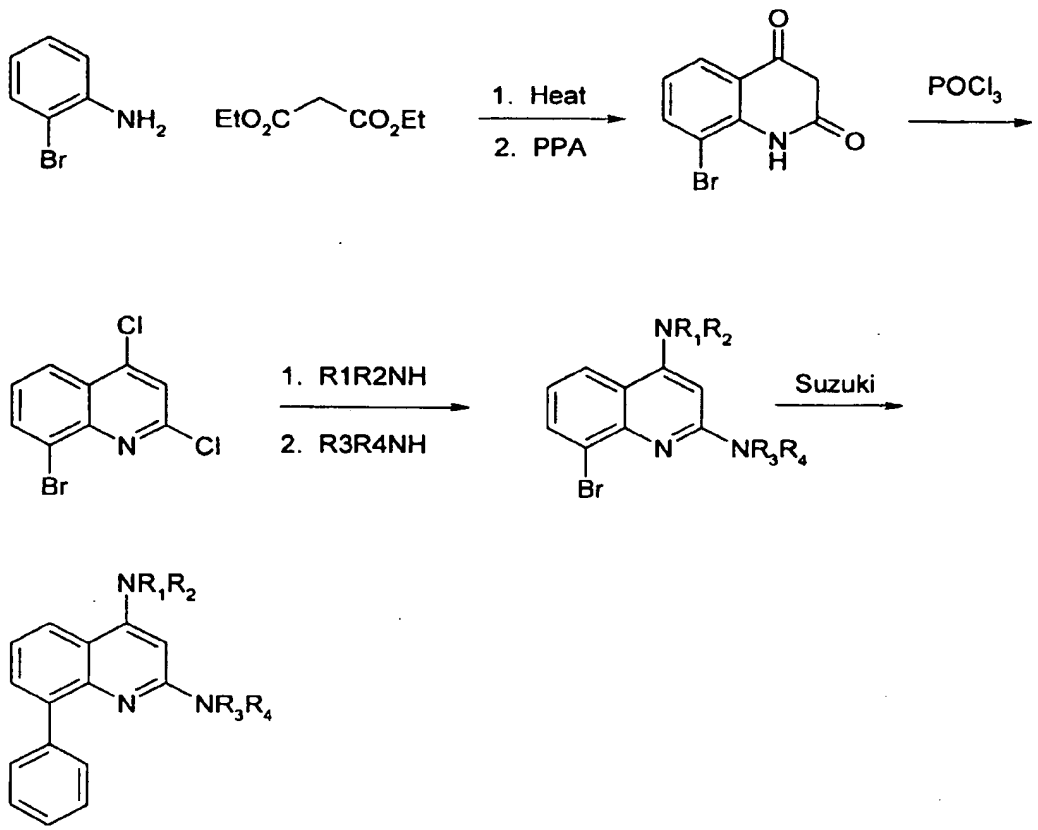
Example 61

Synthesis of Compounds of Formula XIV

Compounds of class CaI represent compounds of Formula XIV wherein R_3, R_6, and R_7 are hydrogen and R_8 is Y_3, as defined herein.



CaI

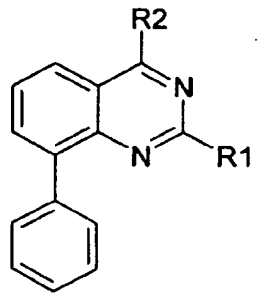


2-bromoaniline is converted into 2,4-dihydroxy-8-bromoquinoline and subsequently into the CaI compounds by methods described earlier.

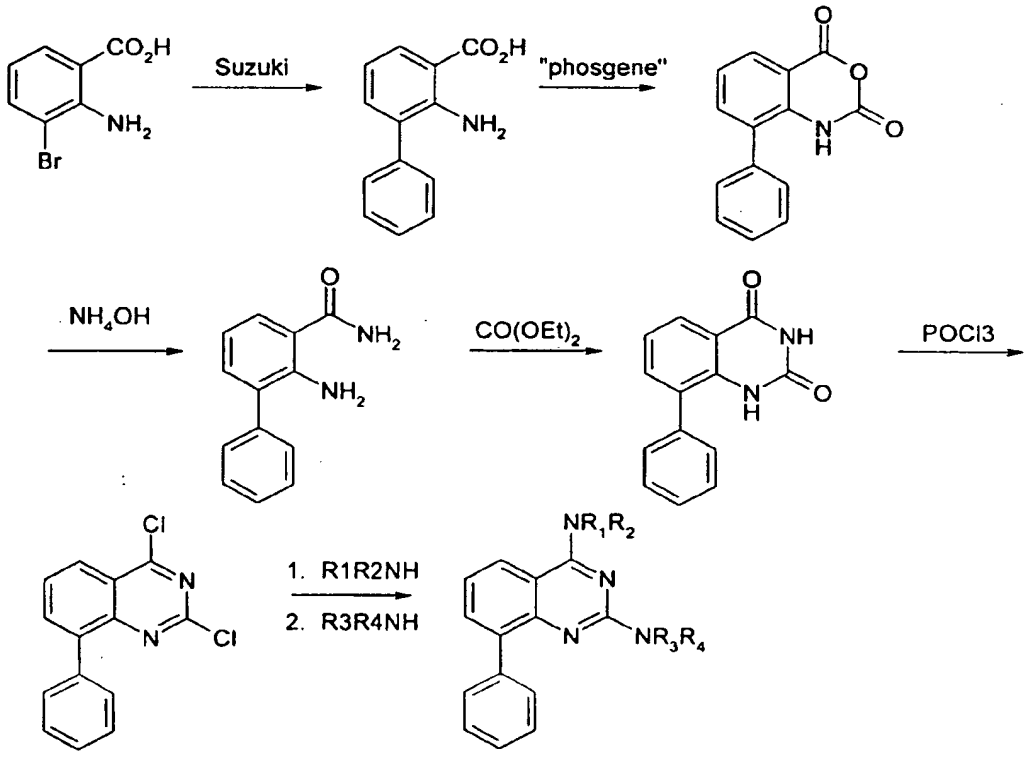
Example 62

Synthesis of Compounds of Formula XV

Compounds of class A3I represent compounds of Formula XV wherein R_6 and R_7 are hydrogen and R_8 is Y_3, as defined herein.



CaII



3-bromoanthranilic acid is converted to 3-phenylanthranilic acid by Suzuki coupling procedures described above. The 3-phenylanthranilic acid is used to prepare the isatoic anhydride by reaction with a phosgene equivalent. Ring opening with ammonium hydroxide provides the anthranilamide which is converted to the dihydroxyquinazoline by the methods described earlier. Conversion to the dichloroquinazoline followed by sequential displacement of the chlorine in the 4-position of the quinazoline and displacement of the chlorine in the 2-position by the same or different amines provides the CaII compounds.

Example 63

In Vitro Testing

Peripheral blood mononuclear cell (PBMC) buffy coat preparations from healthy male and female human donors were obtained from the Institute for Hemostaseology and Transfusion Medicine of the University of Düsseldorf (Germany).

PBMC were purified by centrifugation over Ficoll-Hypaque (Sigma). Purified PBMC were washed twice with 1xPBS and resuspended in RPMI 1640 culture medium supplemented with 5% (v/v) heat-inactivated human AB serum (BioWhittaker, Belgium) or 10% (v/v) heat-inactivated fetal calf serum (FCS), 1.5 mM L-glutamine, 100 U/ml penicillin and 100 mg/ml streptomycin (all from Sigma, Deisenhofen, Germany).

Freshly isolated PBMC were resuspended at a concentration of $3x10^6$/ml to $5x10^6$/ml with RPMI 1640 culture medium and added to 96-well round-bottomed plates (150 µl/well) which had previously received nothing or selected concentrations (typically 10 µM – 0.085 nM as 7-fold serial dilutions) of small molecule. To assay antagonist reaction for TLR9, 1 µM CpG oligodeoxynucleotide (ODN) 2395 (TCGTCGTTTTCGGCGCGCGCCG; SEQ ID NO:3) was added to wells containing small molecules. To assay antagonist reaction for TLR7 and TLR8, 0.5 µM oligoribonucleotide (ORN) R-1362 (UUGUUGUUGUUGUUGUUGUU; SEQ ID NO:4) complexed to 5 µg/ml DOTAP was added to wells containing small molecules. To calculate response to CpG ODN 2395 alone or ORN R-1362+DOTAP alone, wells without small molecules were stimulated with CpG ODN 2395 or ORN R-1362+DOTAP.

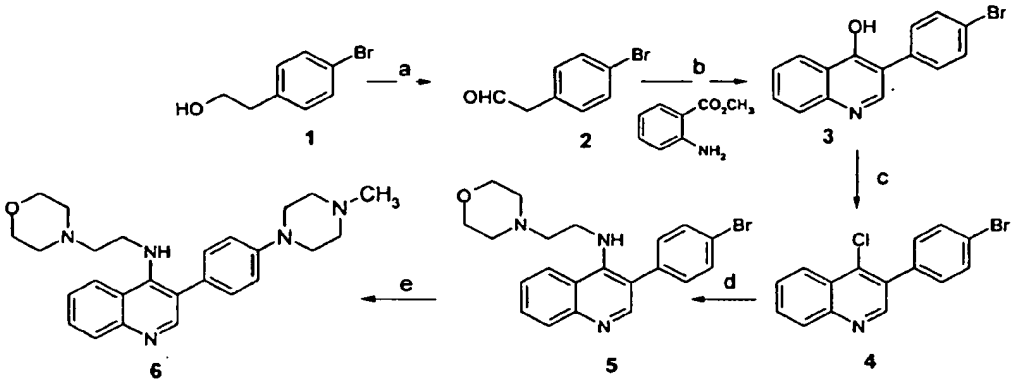
Cells were cultured in a humidified incubator at 37 °C for 16h. Culture supernatants were then collected and, if not used immediately, frozen at –20 °C until required.

Amounts of cytokines in the supernatants were assessed using enzyme-linked immunosorbent assays (ELISA) specific for IFN-α or TNF-α using commercially available antibodies or kits from BD Pharmingen or Diaclone, respectively. IFN-α readout using CpG 2395 was used to measure TLR9 response. IFN-α readout using

ORN R-1362+DOTAP was used to measure TLR7 response. TNF-α release using R-1362 complexed to DOTAP was used to measure TLR8-mediated immune response.

Example 64

Synthesis and In Vitro Characterization of a Compound from Example 4



Reagents and Conditions; a) Dess-Martin, b) amine then KHMDS, c) POCl3, d) amine, e) Buchwald

Synthesis of 2:

A solution of p-bromophenethyl alcohol (2.23 g, 11.5 mmol) in dichloromethane (DCM) (20 mL) was treated with Dess-Martin reagent (6.5 g) at room temperature. After stirring at room temperature overnight, the solution was diluted with DCM (100 mL), washed with saturated $NaHCO_3$, dried (Na_2SO_4), and purified by column chromatography (EtOAc:hexane = 20:80) to provide the aldehyde **2** (1.0 g, 43%).

Synthesis of 3:

A mixture of the aldehyde **2** (1.0 g, 5 mmol) with methylanthranilate (1.03 g, 6.8 mmol) in toluene (1 mL) was stirred at room temperature for 2h. To the formed solid was added additional toluene (6 mL) and ethyl acetate(EtOAc) (5 mL), which was filtered, washed with hexane, and dried under vacuum to provide the imine (700 mg).

To a stirred solution of the imine (700 mg) in tetrahydrofuran (THF) (10 mL) was added potassium hexamethyldisilazide (KHMDS) (6.6 mL of 0.5M/tolune, 3.3

mmol) at -78 °C. The resulting dark solution was warmed to room temperature and stirred for 2h. To the solution was added H_2O (10 mL) and the solvents were removed under vacuum. The resulting residue was purified by column chromatography to provide **3** (120 mg, ~8%).

Synthesis of 4:

A mixture of **3** (114 mg, 0.4 mmol) with $POCl_3$ (2 mL) was heated at 100 °C for 4h. After pouring into ice/H_2O (10 mL), the mixture was extracted with dichloromethane (20 mL) followed by EtOAc (20 mL). The combined organic extracts were dried (Na_2SO_4), passed through a short pad of SiO_2, and concentrated to provide **4** (142 mg, 100%) as a brown solid. Without further purification this solid **4** was used for the next reaction.

Synthesis of 5:

To a screw-capped vial was placed **4** (142 mg, 0.4 mmol), followed by N-methylpyrrolidinone (NMP) (3 mL), 2-morpholinoethanamine (160 mg), and diisopropylethylamine (DIEA) (200 μL). The resulting solution was heated at 160 °C for 24h. After concentration, the resulting residue was diluted with EtOAc (100 mL), washed with saturated $NaHCO_3$ (50 mL), dried (Na_2SO_4), and concentrated to give a brown solid, which was purified by flash chromatography (hexane:EtOAc = 50:50 to 0:100) to provide crude product **5** which was used for the next reaction.

Synthesis of 6 (A3I):

To a screw-capped vial was placed above **5**, followed by toluene (3 mL), KO-t-Bu (110 mg), tris(dibenzylideneacetone)dipalladium (0) [$Pd_2(dba)_3$] (34 mg), and 2-(di-tert-butylphosphino)biphenyl (22 mg), and N-methylpiperazine (124 μL). The suspension was flushed again with N_2, capped, and the resulting suspension was heated at 100 °C for 2 days. The solution was extracted with EtOAc (20 mL). Organic extract was dried (Na_2SO_4) and purified by preparative TLC (DCM:MeOH = 80:20) to provide **6**. ^1H NMR (CD_3OD, 400 MHz) δ 2.25 (br, 4H), 2.35 (s, 3H), 2.39 (t, 2H), 2.63 (t, 4H), 3.26 (m, overlapped with solvent, 4H + 2H), 3.49 (t, 4H), 7.10

(d, 2H), 7.35 (d, 2H), 7.51 (t, 1H), 7.66 (t, 1H), 7.84 (d, 1H), 8.20 (d, 1H), 8.27 (s, 1H); LC/MS ES+ 432 (M+1), >95% pure.

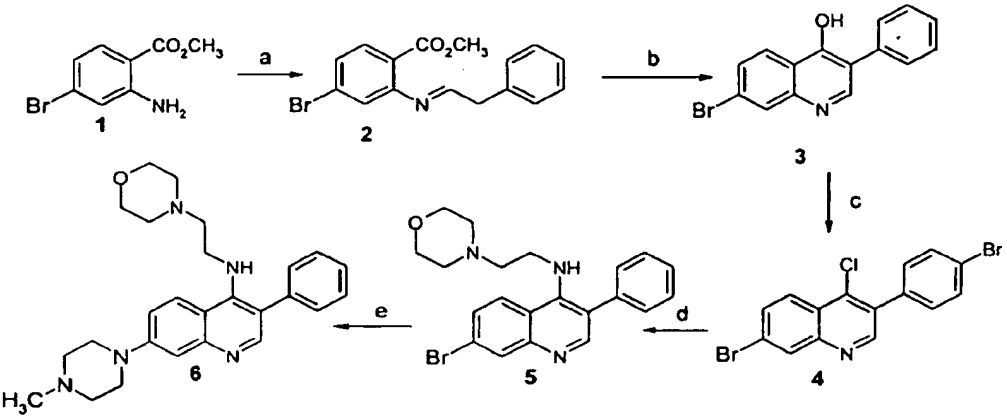
In Vitro Characterization of 6 (A3I):

Compound 6 in this example corresponds to a compound of Formula III with R_6, R_7 and R_8 = H; $R_3 = Y_1$ (Ar-Y_2), Y_2 = pip; R_4 = dimor. See Example 4, Table 4, Y_2 = pip and R_4 = dimor. In vitro testing as described in Example 63 yielded the following results, expressed as IC_{50} (nM):

	TLR7	TLR8	TLR9
Experimental	720	110	73
Calculated			75

Example 65

Synthesis and In Vitro Characterization of a Compound from Example 6



Reagents and Conditions; a) phenylacetaldehyde, b) LDA c) POCl3, d) amine, e) Buchwald

Synthesis of 3:

A mixture of 1 (2.3 g, 10 mmol) with phenylacetaldehyde (2.3 mL, 20 mmol) was stirred at room temperature for 2h. The solid which formed was filtered, washed with hexane, and dried to provide 2. Without further purification the product was used for the next reaction.

To a stirred solution of above **2** in THF (30 mL) was added lithium diisopropylamide (LDA) (5.5 mL of 2M/heptane/THF/ethylbenzene, 11 mmol) at -78 °C. The resulting dark solution was warmed to room temperature and stirred for 2h. To the solution was added H_2O (10 mL) and the organic layer was removed. The resulting residue was purified by column chromatography to provide **3** (540 mg, 26%) as a solid.

Synthesis of 4:

Above **3** (540 mg, 1.8 mmol) with $POCl_3$ (5 mL) was heated at reflux overnight. After pouring into ice/H_2O (10 mL), the mixture was extracted with dichloromethane (20 mL) followed by EtOAc (20 mL). The combined organic extracts were dried (Na_2SO_4), passed through a short pad of SiO_2, and concentrated to provide **4**. The crude product was purified by flash chromatography (EtOAc:hexane = 10:90) to provide **4** (270 mg, 47%) as a solid.

Synthesis of 5:

To a screw-capped vial was placed **4** (270 mg, 0.85 mmol), followed by NMP (1 mL), 2-morpholinoethanamine (500 mg), and diisopropylethylamine (200 μL). The resulting solution was heated at 170 °C for 18h. After concentration, the resulting residue was diluted with EtOAc (100 mL), washed with saturated $NaHCO_3$ (50 mL), dried (Na_2SO_4), and concentrated to give a brown solid, which was purified by flash chromatography (EtOAc:hexane = 80:20 to 100:0) to provide **5** (173 mg, 49%) as a solid.

Synthesis of 6 (AbI):

To a screw-capped vial was placed above **5** (82 mg, 0.2 mmol), followed by toluene (3 mL), KO-t-Bu (34 mg, 0.3 mmol), $Pd(OAc)_2$ (3 mg), N-methylpiperazine (20 mg, 0.2 mmol) and 2-(di-tert-butylphosphino)biphenyl (6 mg). After heating at 100 °C for 2h, the solution was subjected to purification by column chromatography (MeOH:DCM = 20:80) to give **6** (22 mg, 26%). A second batch was carried out to obtained additional **6** (~20 mg). ^1H NMR (CD_3OD, 400 MHz) δ 2.25 (br, 4H), 2.38

(br, 2H + 3H), 2.68 (br, 4H), 3.09 (t, 2H, J = 6.4Hz), 3.36 (br, 4H), 3.49 (br, 4H), 7.3-7.6 (set of m, 7H), 7.77 (d, 1H, J = 8.8Hz), 8.12 (s, 1H); ES+ 334 (M+1), >95% pure.

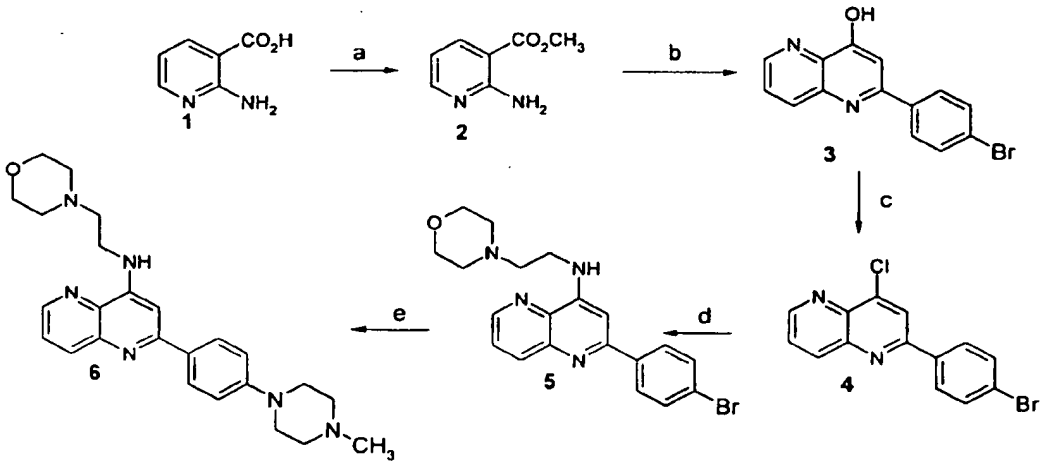
In Vitro Characterization of 6 (AbI):

Compound 6 in this example corresponds to a compound of Formula III with R_6 and R_8 = H; R_3 = Y_3 = phenyl; R_7 = Y_2 = pip; and R_4 = dimor. See Example 6, Table 6, Y_2 = pip and R_4 = dimor. In vitro testing as described in Example 63 yielded the following results, expressed as IC_{50} (nM):

	TLR7	TLR8	TLR9
Experimental	180	160	160
Calculated			750

Example 66

Synthesis and In Vitro Characterization of a Compound from Example 31



Reagents and Conditions; a) MeOH, conc. H2SO4, b) 4-bromoacetophenone, NaOtBu, c) POCl3, d) amine, e) Buchwald

Synthesis of 2:

A mixture of 1 (2.0 g, 14 mmol) in concentrated H_2SO_4 (a few drops) in MeOH (5 mL) was heated at reflux overnight. After concentration the residue was taken up into EtOAc, washed with saturated $NaHCO_3$, H_2O, and dried (Na_2SO_4) to provide 2 (400 mg, 20%) as a yellow solid.

Synthesis of 3:

To a stirred solution of NaO-*t*-Bu (253 mg, 2.6 mmol) in dry THF (5 mL) was added 4-bromoacetophenone (131 mg, 0.66 mmol) at 0 °C under N_2. To this solution was added **2** (100 mg, 0.66 mmol) at the same temperature. The reaction was warmed to room temperature and stirred overnight. After addition of H_2O (1 mL), the solution was extracted with EtOAc (20 mL). The organic extract was dried (Na_2SO_4) and concentrated to give a dark brown semi-solid, which was subjected to purification by preparative thin layer chromatography (TLC) ($CHCl_3$:MeOH = 90:10 with 1% of NH_4OH) to obtain **3** (30mg, 15%) as a pale yellow film. A mass of 301(mass +1) was determined for this compound by liquid chromatography/mass spectroscopy. [LC/MS 301(M+1)]

Synthesis of 4:

A mixture of **3** (22 mg, 0.07 mmol) with $POCl_3$ (1.5 mL) and 2,6-lutidine (0.7 mL) was heated at 90 °C for 16h. After pouring into ice/H_2O (10 mL), the mixture was extracted with dichloromethane (20 mL) followed by EtOAc (20 mL). The combined organic extracts were dried (Na_2SO_4), passed through a short pad of SiO_2, and concentrated to provide **4** (25 mg) which was used for the next reaction.

Synthesis of 5:

To a screw-capped vial was placed **4** (25 mg, 0.07 mmol), followed by NMP (2 mL), 2-morpholinoethanamine (30 mg). Resulting solution was heated at 170 °C for 16h. After dilution with EtOAc, the solution was washed with brine (3x), dried (Na_2SO_4) to obtain **5** (18 mg, 64%), after purification by column chromatography (dichloromethane/methanol). The compound **5** was used for the next reaction.

Synthesis of 6 (BIV):

To a screw-capped vial was placed above **5** (17 mg, 0.05 mmol), followed by toluene (2 mL), NaO-t-Bu (15 mg), $Pd_2(dba)_3$ (14 mg), and 2-(di-tert-butylphosphino)biphenyl (9 mg), and N-methylpiperazine (17 μL). The reaction was heated at 100 °C for 4h. After dilution with EtOAc (3 mL) and 10% HCl/H_2O (1.5

mL/1.5 mL), the aqueous phase was separated, neutralized by 2N NaOH, and extracted with EtOAc (2x), dried (Na_2SO_4), and concentrated. The residue was then recrystallized with $CHCl_3$ and hexane to provide **6** (11.4 mg, 52%) as a yellow solid. LC/MS ES+ 433 (M+1), >95% pure.

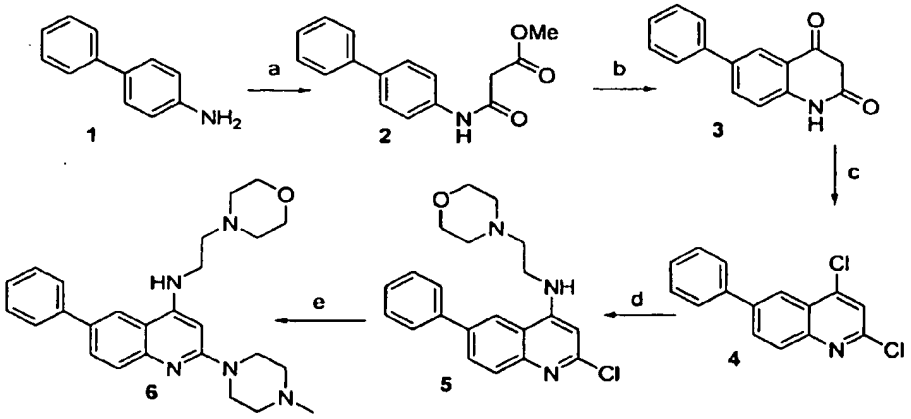
In Vitro Characterization of 6 (BIV):

Compound **6** in this example corresponds to a compound of Formula XI with R_3, R_6, R_7, and R_8 = H; Y_1 = Ar-Y_2 = pip; and R_4 = dimor. See Example 31, Table 31, Y_2 = pip and R_4 = dimor. In vitro testing as described in Example 63 yielded the following results, expressed as IC_{50} (nM):

	TLR7	TLR8	TLR9
Experimental	70	100	44
Calculated			34

Example 67

Synthesis and In Vitro Characterization of a Compound from Example 32



Reagents and Conditions: a) Dimethyl malonate b) $AlCl_3$ c) $POCl_3$. d) amine, NMP e) amine, 150°C

Synthesis of 2:

A mixture of **1** (3.4 g, 23.7 mmol) in dimethylmalonate (16 mL) was heated at refluxed (ca 150-165 °C) for 20h. After concentration, the dark residue was purified

by column chromatography (EtOAc:hexane = 25:75 to 40:60) to provide **2** (4.5 g, 80%).

Synthesis of 3 and 4:

To a stirred solution of **2** (3.3 g, 12.3 mmol) in chlorobenzene (50 mL) was added portion wise $AlCl_3$ (4.9 g, 36 mmol) at 0 °C under a N_2 atmosphere. The resulting solution was heated at 120 °C for 3h. The dark solution was slowly poured into ice/H_2O to provide a precipitate. The solid was collected by filtration, washed with water, and dried to provide **3**.

Without further purification, the product was used for the next reaction.

To the above solid was added $POCl_3$ (15 mL) at room temperature. The resulting solution was heated at reflux for 3h. The reaction was poured into ice/H_2O, and extracted with EtOAc (3x). The combined organic extracts were dried (Na_2SO_4) and purified by flash chromatography (DCM:hexane = 5:95) to obtain **4** (310 mg, 9.2%) as a solid.

Synthesis of 5:

To a screw-capped vial was placed **4** (220 mg, 0.8 mmol), followed by N-methylpyrrolidinone (1.5 mL), 2-morpholinoethanamine (160 mg), and diisopropylethylamine (300 μL). The resulting solution was heated at 100 °C for 16h. After dilution with EtOAc, the solution was washed with brine (3x) and dried (Na_2SO_4) to provide **5** (262 mg, 63%) after purification by flash chromatography (EtOAc:hexane = 80:20 to MeOH:EtOAc = 5:95).

Synthesis of 6 (CI):

To a screw-capped vial was placed **5** (112 mg, 0.3 mmol), followed by N-methylpiperazine (2 mL). The resulting solution was heated at 150 °C for 18h. After dilution with EtOAc, the solution was washed with brine (2x) and dried (Na_2SO_4) to provide **6** (48 mg for first crop and 68mg; second crop, total 87%) after recrystallization with EtOAc/ hexane. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 2.53 (brm, 8H), 2.78 (t, 2H), 3.32 (dd, 2H), 3.73 (br, 8H), 5.74 (br, 1H), 5.93 (s, 1H), 7.32 (t, 1H), 7.44 (t, 2H), 7.72 (set of m, 5H). LC/MS m/e 432 (M+1).

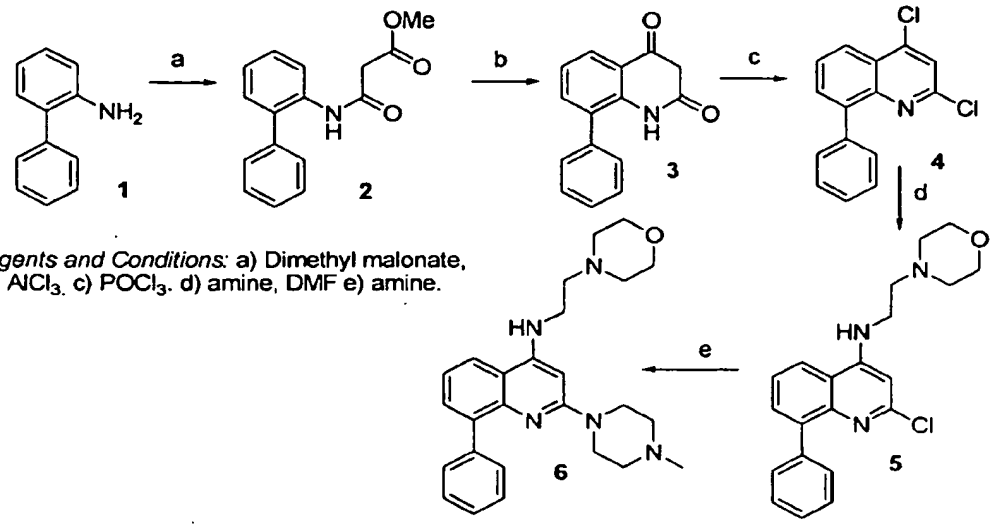
In Vitro Characterization of 6 (CI):

Compound **6** in this example corresponds to a compound of Formula XIV with R_3, R_7, and R_8 = H; R_6 = Y_3 = phenyl; Y_2 = pip; and R_4 = dimor. See Example 32, Table 32, Y_2 = pip and R_4 = dimor. In vitro testing as described in Example 63 yielded the following results, expressed as IC_{50} (nM):

	TLR7	TLR8	TLR9
Experimental	200	600	200
Calculated			570

Example 68

Synthesis and In Vitro Characterization of a Compound from Example 33



Reagents and Conditions: a) Dimethyl malonate, b) $AlCl_3$, c) $POCl_3$, d) amine, DMF e) amine.

Synthesis of 3 and 4:

To a stirred solution of **2** (8.3 g, 31 mmol), which was prepared by the same procedure as described before (Synthesis of CI), in chlorobenzene (80 mL) was added portionwise $AlCl_3$ (12.3 g, 93 mmol) at 0 °C under a N_2 atmosphere. The resulting solution was heated at 110-120 °C for 4h. The dark solution was slowly poured into ice/H_2O with vigorous stirring. The resulting solution was extracted with chloroform (3x). The combined organic extracts were washed with brine and dried (Na_2SO_4).

After concentration, the gummy residue was triturated with EtOAc to afford **3** as a pink powder, which was washed with EtOAc and hexane. Without further purification, the product **3** was used for the next reaction.

To the above **3** was added $POCl_3$ (30 mL) at room temperature. The resulting solution was heated at 80 °C for 4h. The reaction was poured into ice/H_2O (300 mL), and extracted with EtOAc (3x). The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4), and purified by flash chromatography (EtOAc:hexane = 3:97) to provide **4** (310 mg, 3.5%) as a solid.

Synthesis of 5:

To a screw-capped vial was placed **4** (310 mg, 1.1 mmol), followed by N-methylpyrrolidine (3 mL), 2-morpholinoethanamine (160 mg), and diisopropylethylamine (700 μL). The resulting solution was heated at 100 °C for 18h. After dilution with EtOAc, the solution was washed with brine (3x) and dried (Na_2SO_4) to provide **5** (190 mg, 47%) after purification by flash chromatography (EtOAc = 100 to MeOH:EtOAc = 5:95).

Synthesis of 6 (CaI):

To a screw-capped vial was placed **5** (90 mg, 0.24 mmol), followed by N-methylpiperazine (2 mL). The resulting solution was heated at 150 °C for 20h. After dilution with EtOAc, the solution was washed with brine (2x) and dried (Na_2SO_4) to provide **6** (49 mg, 46%) after purification by flash chromatography (EtOAc to MeOH:EtOAc = 10:90). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.39 (s, 3H), 2.53 (br, 4H), 2.58 (br, 4H), 2.78 (t, 2H, J = 5.6Hz), 3.31 (m, 2H), 3.68 (br, 4H), 3.74 (br, 4H), 5.75 (br, 1H), 5.91 (s, 1H), 7.24 (t, 1H, overlapped with solvent), 7.30 (t, 1H), 7.39 (t, 2H), 7.57 (t, 2H), 7.74 (t, 2H). LC/MS 433 (M+1).

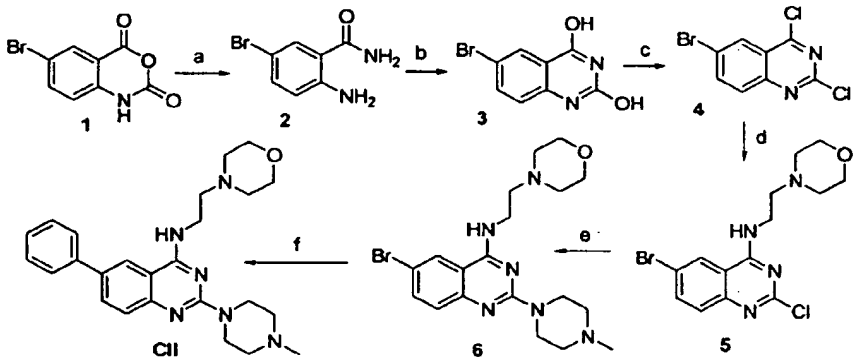
In Vitro Characterization of 6 (CaI):

Compound **6** in this example corresponds to a compound of Formula XIV with R_3, R_6, and R_7 = H; R_8 = Y_3 = phenyl; Y_2 = pip; and R_4 = dimor. See Example 33, Table 33, Y_2 = pip and R_4 = dimor. In vitro testing as described in Example 63 yielded the following results, expressed as IC_{50} (nM):

	TLR7	TLR8	TLR9
Experimental	790	140	250
Calculated			44

Example 69

Synthesis and In Vitro Characterization of a Compound from Example 34



Reagents and Conditions: a) NH_4OH. b) CDI, THF. c) $POCl_3$, 2,6-lutidine, 140°C. d) amine, DIEA, EtOH, 80 °C. e) N-methylpiperazine, isoamylalcohol, 140°C. f) phenylboronic acid, $Pd(OAc)_2$, Bu_4NBr, K_2CO_3, H_2O, 80 °C.

Synthesis of 2:

To a stirred solution of 6-bromoisatoic anhydride **1** (10 g, 41.3 mmol) in THF (500 mL) was added slowly NH_4OH (20 mL) at room temperature. The suspension became clear. The solution was then stirred at room temperature overnight and concentrated to provide a white solid. The resulting solid was collected by filtration, washed with H_2O (~50 mL), and dried to afford **2** (6.7 g, 76%) as an off-white solid.

Synthesis of 3:

A suspension of **2** (500 mg, 2.3 mmol) in THF (6 mL) was treated with 1,1'-carbonyldimidazole (CDI) (410 mg, 2.5 mmol). The resulting suspension was heated at 75 °C overnight. During the reaction, the suspension became clear, then solid was formed. After concentration, the resulting solid was collected, washed with dichloromethane, and dried to afford **3** (450 mg, 82%) as a pale yellow solid. The NMR was consistent with the structure of **3**.

Synthesis of 4:

A solution of **3** (500 mg, 2 mmol) in $POCl_3$ (4 mL) in a vial (15 mL) was treated with 2,6-lutidine (1.3 mL) at room temperature. The resulting suspension was then heated at 140 °C overnight. After pouring into ice/H_2O (10 mL), the mixture was extracted with dichloromethane (20 mL) followed by EtOAc (20 mL). The combined organic extracts were dried (Na_2SO_4), passed through a short pad of SiO_2, and concentrated to provide **4** (390 mg) as a brown solid. Without further purification this solid **4** was used for the next reaction.

Synthesis of 5:

The product obtained as described in the previous step, **4** (2.3 g) was suspended in EtOH (50 mL) and treated with diisopropylethylamine (DIEA) (4 mL), followed by 2-morpholinoethylamine (3 mL) at room temperature. The solution was heated at reflux overnight. After concentration, the resulting residue was diluted with EtOAc (100 mL), washed with saturated $NaHCO_3$ (50 mL), dried (Na_2SO_4), and concentrated to give a brown solid, which was purified by flash chromatography (hexane:EtOAc = 50:50 to 0:100) to provide **5** (350 mg) as a brown solid.

Synthesis of 6:

Monosubstituted quinazoline **5** (320 mg, 0.86 mmol) was dissolved in isoamyl alcohol (5 mL) and distributed equally into two vials (15 mL capacity). Each vial was treated with N-methylpiperazine (200 μL). The resulting solution was heated at 140 °C overnight. After concentration, the resulting solid was purified by flash chromatography (EtOAc to DCM:MeOH = 95:5 to 80:20) to provide **6** (120 mg) as a solid.

Synthesis of CII:

The above solid **6** (120 mg, 0.27 mmol) was placed in a vial (15 mL capacity), followed by phenylboronic acid (66 mg, 0.5 mmol), $Pd(OAc)_2$ (2 mg), K_2CO_3 (140 mg, 1 mmol), and Bu_4NBr (12 mg, 0.35 mmol). The mixture was flushed with N_2 and to this was added H_2O (4 mL) and toluene (2 mL). The suspension was flushed again with N_2 and capped. The resulting suspension was heated at 100 °C for 2 days. The

mixture was extracted with EtOAc (20 mL). The organic extract was dried (Na_2SO_4) and purified by preparative TLC (DCM:MeOH = 80:20) to provide **CII** (35 mg, 30%) a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 2.53 (br, 4H + 4H), 2.70 (t, 2H), 3.67 (dd, 2H), 3.74 (t, 4H), 3.97 (br, 4H), 7.3-7.8 (set of t, d, s, 8H, aromatic H); LC/MS 433 (M+1), >98% pure.

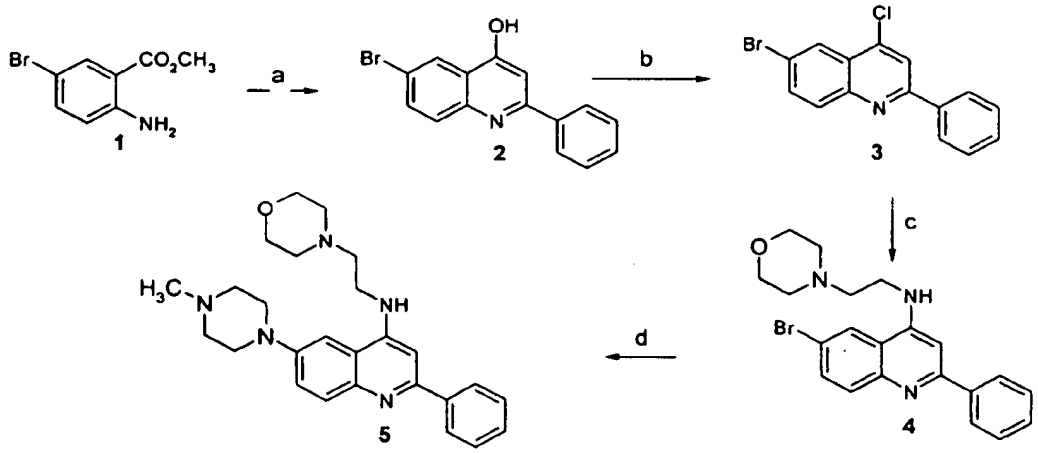
In Vitro Characterization of CII:

Compound **CII** in this example corresponds to a compound of Formula XV with R_7 and R_8 = H; R_6 = Y_3 = phenyl; Y_2 = pip; and R_4 = dimor. See Example 34, Table 34, Y_2 = pip and R_4 = dimor. In vitro testing as described in Example 63 yielded the following results, expressed as IC_{50} (nM):

	TLR7	TLR8	TLR9
Experimental	630	500	100
Calculated			190

Example 70

Synthesis and In Vitro Characterization of a Compound from Example 39



Reagents and Conditions; a) acetophenone, potassium hexamethyldisilazide (KHMDS), b) POCl3, c) amine, d) Buchwald

Synthesis of 2:

To a stirred solution of KHMDS (4 equivalents) in dry THF was added acetophenone (1 equivalent) at 0 °C under N_2. To this solution was added **1** (1 equivalent) at the same temperature. The reaction was warmed to room temperature and stirred overnight. The reaction was worked up as described for the synthesis of **BIV** (See below).

Synthesis of 3:

Synthesis of **3** from **2** was carried out as described in Example 66 for the synthesis of **6 (BIV)**.

Synthesis of 4:

Synthesis of **4** from **3** was carried out as described in Example 66 for the synthesis of **6 (BIV)**.

Synthesis of 5:

Synthesis of **5** from **4** was carried out as described in Example 66 for the synthesis of **6 (BIV)**. MS 432 (M+1), >95% pure.

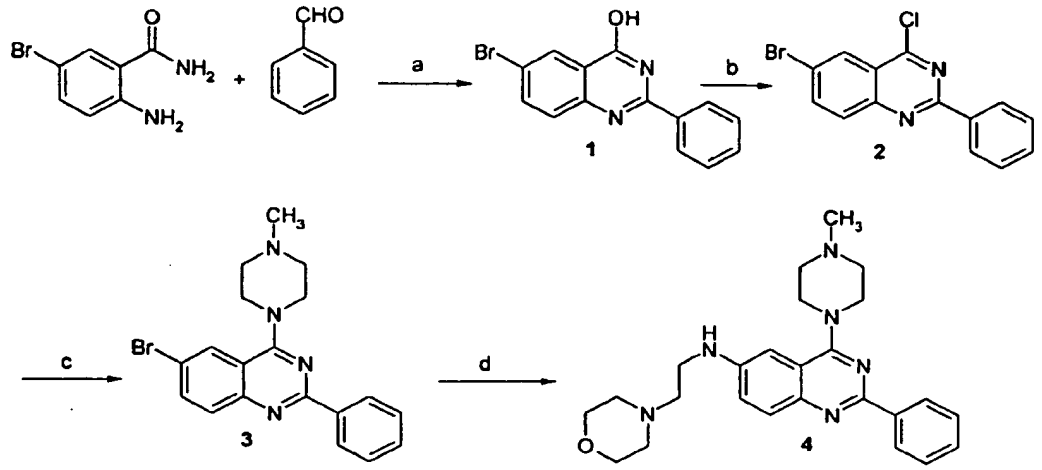
In Vitro Characterization of 5 (DI):

Compound **5** in this example corresponds to a compound of Formula XX with R_3, R_7, and R_8 = H; Y_3 = phenyl; R_6 = Y_2 = pip; and R_4 = dimor. See Example 39, Table 39, Y_2 = pip and R_4 = dimor. In vitro testing as described in Example 63 yielded the following results, expressed as IC_{50} (nM):

	TLR7	TLR8	TLR9
Experimental	75	28	72
Calculated			17

Example 71

Synthesis and In Vitro Characterization of a Compound from Example 40



reagents and conditions: a) $Na_2S_2O_5$ b) $POCl_3$ c) N-methylpiperazine, d) aminoethylmorpholine, Pd(0)

Synthesis of 1:

A mixture of 5-bromoanthranilamide (7.5 g, 3.49 mmol), benzaldehyde (3.7 g, 3.49 mmol), sodium metabisulfite (4.98 g, 26.2 mmol) and water (0.5 mL) in dimethylacetamide was stirred at 150 °C for 2h. After this time, the slurry was cooled to 50 °C and water (200 mL) was added. This slurry was stirred for 10 minutes and was then filtered to isolate the product. The filter cake was washed with water and was then, while still damp, recrystallized from DMF. The yield of purified **1** was 4.45 g (42.3%).

Synthesis of 2 and 3:

A slurry of 2-phenyl-6-bromoquinazolin-4-one (4.44 g, 14.7 mmol) in 1,2-dichlorobenzene (40 mL) was stirred at 130 °C as phosphorous oxychloride (4.52 g, 29.5 mmol) was added over 5 minutes. This mixture was stirred at 130 °C until a clear, pale orange solution formed (about 90 minutes) and then for an additional 30 minutes longer. After cooling, the solution was diluted with t-butylmethyl ether (200 mL) and this solution was shaken with water (200 mL). The aqueous phase was discarded and the tert-butylmethyl ether (TBME) solution was washed with a solution of sodium hydroxide (5.9 g) in water (200 mL). The TBME was then evaporated to give a slurry of **2** in 1,2-dichlorobenzene. This slurry was diluted with n-butanol (40 mL) and N-methylpiperazine (4.40 g, 44 mmol) was added. This mixture was heated

to reflux which provided a clear yellow solution. The reaction was examined by TLC (silica, 10% methanol in methylene chloride) after 30 minutes at reflux and was found to have gone to completion. The solution was cooled and diluted with TBME (200 mL). This solution was extracted with 10% HCl (150 mL) and the acidic extracts were then made basic by the addition of 10% sodium hydroxide solution. The product that separated from the basic mixture was extracted into methylene chloride (200 mL). Evaporation of the methylene chloride under vacuum gave the product **3** as an oil in a yield of 5.2 g (92%). The oil was dissolved in hexane (25 mL) from which it crystallized as a white powder.

Synthesis of 4:

The bromoquinazoline **3** (1.0 g, 2.6 mmol) was combined with tris-(dibenzylideneacetone)dipalladium (0) (23.8 mg, 2.6 X 10^{-5} mol), +/- binaphthyl (BINAP) (48.6 mg, 7.8 X 10^{-5} mol), sodium tert-butoxide (350 mg, 3.6 mmol) and toluene (5 mL). This mixture was stirred under nitrogen for 15 minutes and was then treated with 2-aminoethylmorpholine (406 mg, 3.12 mmol) in toluene (3 mL). The reaction was then stirred under nitrogen for 2h. The reaction was examined by TLC (silica, 10% methanol in methylene chloride) after this time and was found to have gone to completion. After cooling, the reaction mixture was diluted with ethyl acetate (100 mL) and was washed with water (100 mL). The ethyl acetate solution was then extracted with 10% HCl (2 X 25 mL). The yellow acidic extracts were combined and were washed with ethyl acetate (25 mL) after which they were made basic by the addition of 10% sodium hydroxide solution. The solid which precipitated was extracted into methylene chloride (2 X 25 mL). Evaporation of the solvents gave the product **4** as a yellow solid in a yield of 1.02 g (90.7%). This solid was recrystallized from a mixture of toluene and hexane.

In Vitro Characterization of 4:

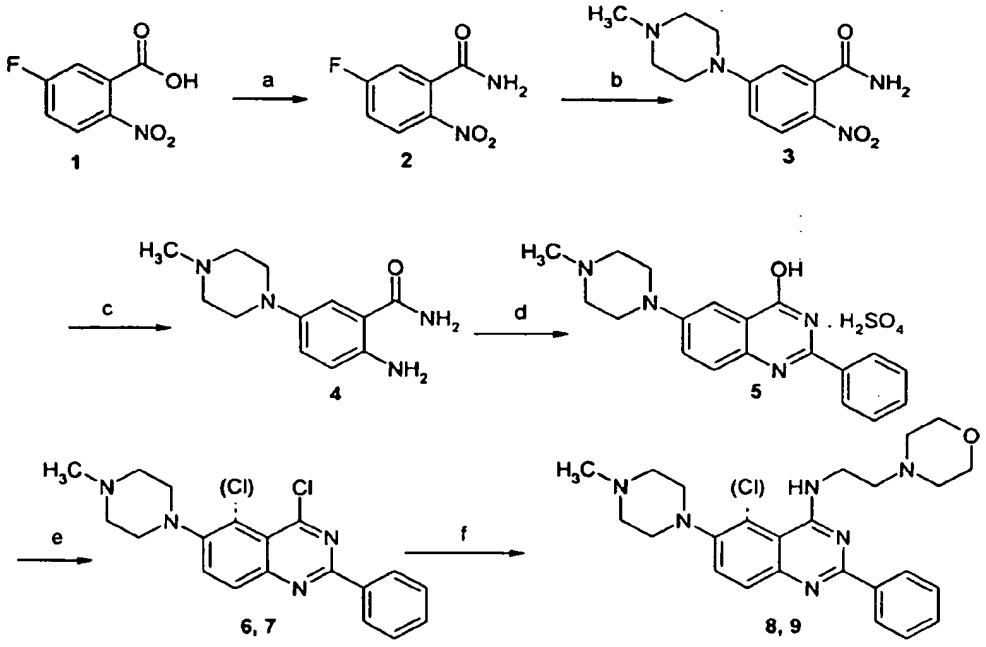
Compound **4** in this example corresponds to a compound of Formula XXI with R_7 and R_8 = H; Y_3 = phenyl; R_6 = Y_2 = dimor; and R_4 = pip. See Example 40, Table 40, Y_2 = dimor and R_4 = pip. In vitro testing as described in Example 63 yielded the following results, expressed as IC_{50} (nM):

	TLR7	TLR8	TLR9
Experimental	170	ND*	53
Calculated			33

* not done

Example 72

Synthesis and In Vitro Characterization of a Compound from Example 40



Reagents and Conditions; a) $SOCl_2$, NH_4OH b) N-methylpiperazine c) NH_4CO_2H, Pd/C d) benzaldehyde, H_2SO_4, chloranil e) $POCl_3$ f) 2-aminoethylmorpholine

Synthesis of 2:

To a suspension of 2-nitro-5-fluorobenzoic acid (20 g, 0.108 mol) in methylene chloride (150 mL) was added thionyl chloride (14.3 g, 0.12 mol) and DMF (1 mL). This mixture was stirred at reflux until a clear solution formed (120 min) and then for 30 minutes longer. After cooling the solution was dripped into a well stirred

mixture of methylene chloride (200 mL), concentrated ammonium hydroxide (200 mL) and ice (200 g). After the addition was complete, the mixture was stirred for 30 minutes. The solid amide was isolated by filtration and was washed with water. After drying at 70 °C the 2-nitro-5-fluorobenzamide **2** was obtained as a white solid in a yield of 6.6 g (33%).

Synthesis of 3:

A mixture of 2-nitro-5-fluorobenzamide **2** (6.6 g, 0.036 mol) and N-methylpiperazine (7.25 g, 0.072 mol) in n-butanol (100 mL) was stirred at reflux for 12h. After cooling, the mixture was diluted with ethyl acetate (200 mL) and was then extracted with 5% HCl (2 X 200 mL). The combined extracts were neutralized with sodium bicarbonate and the resulting yellow solution was treated with solid potassium acetate (20 g). After stirring at room temperature for 30 minutes the crystalline product, which had separated, was isolated by filtration. The yellow solid was washed with cold water and dried at 70 °C. The yield of **3** was 4.1 g (43.1%). The compound was shown to be >99% purity by HPLC and the mass spec gave the correct molecular ion.

Synthesis of 4 and 5:

A suspension of N-methyl-N'-(3-carboxamido-4-nitro)piperazine **3** (4.1 g, 15.5 mmol) in ethanol (100 mL) was treated with 10% palladium on carbon (500 mg) and was stirred at reflux. A solution of ammonium formate (2.92 g, 46.4 mmol) in water (5 mL) was added over a one minute period and the resulting mixture was stirred at reflux for 2h. TLC (silica, 10% methanol in methylene chloride) showed that the reaction had gone to completion. The reaction was cooled and the catalyst was removed by filtration. To the filtrates was added benzaldehyde (1.65 g, 15.5 mmol) and 5 drops of concentrated sulfuric acid. This mixture was refluxed for 5 minutes and then cooled. The ethanol was removed under vacuum and dimethylacetamide (100 mL) was added. To this solution was added concentrated sulfuric acid until an orange coloration formed which did not immediately fade (about 2 g). The solution was heated to 90 °C with stirring and chloranil (3.8 g, 15.5 mmol) was added in portions over 2 minutes. Heating was continued for 15 minutes after

which the reaction mixture was allowed to cool to room temperature. The quinazoline sulfate salt **5** crystallized as small pale green needles and was isolated by filtration. The solid was washed with ethanol and dried at 70 °C to give the product in a yield of 4.1 g, (63.2%).

Synthesis of 6, 7, 8 and 9:

Phosphorous oxychloride (30 mL) and the quinazoline sulfate salt **5** (4.1 g, 9.8 mmol) were stirred together as diisopropylethyl amine (3.8 g, 29 mmol) was slowly added. The resulting warm yellow suspension was stirred at reflux for 90 minutes. At this time, TLC (silica, 10% methanol in methylene chloride) showed that the reaction had gone to completion. Excess phosphorous oxychloride (about 15 mL) was removed by distillation and the residue was cautiously added to water (200 mL), ice (200 g), and sodium bicarbonate (60 g) with vigorous stirring. The addition was at a rate that controlled foaming. Once the reaction mixture had been added, stirring was continued for 30 minutes. The solid precipitate was extracted into methylene chloride (200 mL) and this solution was dried over magnesium sulfate. After filtration, the methylene chloride was evaporated to give a mixture of **6** and **7** as a white solid (2.8 g). This material was combined with N-2-aminoethylmorpholine (2.15 g, 16.6 mmol) in n-butanol (100 mL). The mixture was stirred at reflux for 5h. After cooling, the reaction mixture was partitioned between ethyl acetate (200 mL) and 2% potassium carbonate solution (200 mL). The ethyl acetate solution was isolated and extracted with warm 5% HCl (300 mL). The acidic extracts were washed with ethyl acetate (2 X 100 mL) and were then made basic by the addition of solid potassium carbonate. The oil which precipitated was extracted into methylene chloride (200 mL) and these extracts were evaporated under vacuum to provide a mixture of **8** and **9** as an oil which crystallized on standing. HPLC/mass spec analysis of the oil showed that it consisted of a mixture of **8** (47.7%) and **9** (52.3%) in a total yield of 3.5 g. Compounds **8** and **9** were separated by column chromatography on silica using methylene chloride (100 mL) followed by 5% methanol in methylene chloride (500 mL) and 10% methanol in methylene chloride (500 mL) as eluent. HPLC showed that compound **8** was isolated with an HPLC purity of 100% and compound **9** with an HPLC purity of 99.4%. Mass spec and NMR were used to

identify compound **8** as the quinazoline, unsubstituted at position 5, and compound **9** as the 5-chloro derivative.

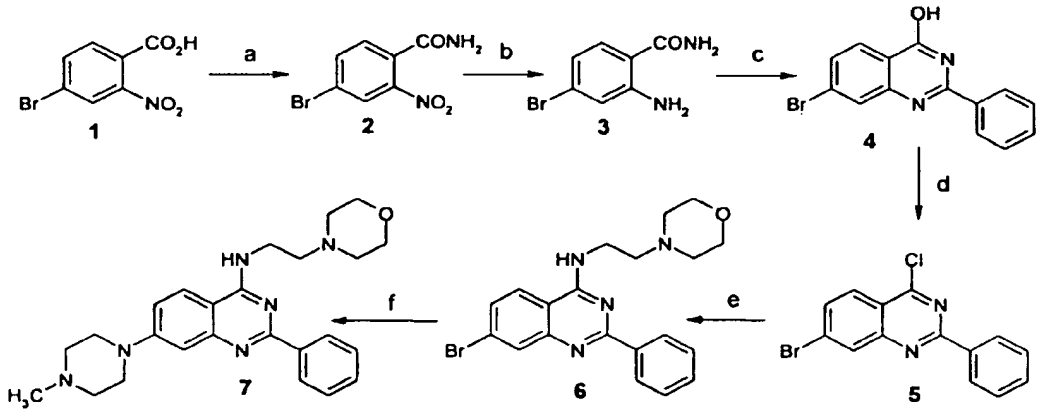
In Vitro Characterization of 8:

Compound **8** in this example corresponds to a compound of Formula XXI with R_7 and R_8 = H; Y_3 = phenyl; R_6 = Y_2 = pip; and R_4 = dimor. See Example 40, Table 40, Y_2 = pip and R_4 = dimor. In vitro testing as described in Example 63 yielded the following results, expressed as IC_{50} (nM):

	TLR7	TLR8	TLR9
Experimental	76	18	78
Calculated			18

Example 73

Synthesis and In Vitro Characterization of a Compound from Example 41



reagents and conditions; a) $SOCl_2$, NH_4OH b) $SnCl_2$ c) benzaldehyde, $NaHSO_3$ d) $POCl_3$ e) amine f) Buchwald

Synthesis of 2:

To a stirred solution of 4-bromo-2-nitrobenzoic acid (3.0 g, 12.2 mmol) in $CHCl_3$ (20 mL) was added thionyl chloride (1.1 mL, 14.6 mmol) at room temperature.

Heating at reflux was continued until a clear solution formed. This solution was used for the next step.

To a stirred mixture of NH_4OH (85 mL of 35% solution) in $CHCl_3$ (25 mL) was added dropwise the above acid chloride solution at ca -25 °C. After stirring at 0 °C for 15 min the reaction mixture was poured onto ice cold water. The solid obtained was filtered, washed with H_2O, and dried to provide **2** (3.09 g) as a white solid.

Synthesis of 3:

A mixture of **2** (2.0 g, 10.6 mmol) in EtOAc (200 mL) was treated with $SnCl_2$ (9.4 g, 42 mmol) at reflux for 20 min. After addition of 1N NaOH, the formed solid was filtered and washed with EtOAc. The organic phase was separated. The aqueous phase was neutralized (pH~7) and extracted with EtOAc (2 x 70 mL). The combined organic extracts were concentrated to provide **3** (1.53 g, 67%) as a tan solid.

Synthesis of 4:

A mixture of **3** (1.5 g, 7.2 mmol) with benzaldehyde (0.73 mL, 7.2 mmol) and sodium bisulfite (1.1 g, 10.8 mmol) in dimethylacetamide (DMA) (5 mL) was heated at reflux for 3h. After pouring into H_2O (20 mL), the solution was allowed to warm up to room temperature. The solid which formed was filtered, washed with H_2O, followed by Et_2O to provide **4** (1.5 g, 69%) as a yellow solid, after recrystallization with MeOH/EtOAc.

Synthesis of 5:

A mixture of **4** (1.5 g, 4.9 mmol) in $POCl_3$ (5 mL) was heated at reflux overnight. After cooling to room temperature, the dark solution was poured into H_2O/ice. The resulting solid was filtered, washed with H_2O, followed by Et_2O to provide **5** (900 mg) as brown yellow solid. Evaporation of the filtrates provided an additional amount of **5** (400 mg) after concentration and trituration with EtOAc/hexane.

Synthesis of 6:

To a screw-capped vial was placed **5** (200 mg, 0.63 mmol) in EtOH (0.5 mL), followed by 2-morpholinoethanamine (100 mg, 0.75 mmol). The resulting solution was heated at 80 °C for 3h. After concentration, the residue was purified by preparative TLC (MeOH:EtOAc = 20:80) to provide **6** (90 mg, 35%) as a yellow solid.

Synthesis of 7 (DbII):

To a screw-capped vial was placed **6** (90 mg, 0.22 mmol), followed by NaO-t-Bu (25 mg, 0.26 mmol), N-methylpiperazine (0.29 mL, 0.26 mmol), $Pd_2(dba)_3$ (4 mg, 0.005 mmol), +/- 2,2'-bis(diphenylphosphiono-1,1'binaphthalene, (BINAP) (4 mg, 0.007 mmol), and toluene (1 mL). After degassing with nitrogen the suspension was heated at 80 °C overnight. After concentration, the residue was filtered through a short pad of SiO_2 to provide **7** (32 mg, 35%) after purification by preparative TLC (MeOH:EtOAc = 20:80). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (s, 3H), 2.58 (br, 4H + 4H), 2.77 (t, 2H), 3.40 (br, 4H), 3.75 (t, 4H), 3.85 (dd, 2H), 7.0-8.5 (set of t, d, s, 8H, aromatic H); LC/MS: 433 (M+1), >98% pure.

In Vitro Characterization of 7 (DbII):

Compound **7** in this example corresponds to a compound of Formula XXI with R_6 and R_8 = H; Y_3 = phenyl; R_7 = Y_2 = pip; and R_4 = dimor. See Example 41, Table 41, Y_2 = pip and R_4 = dimor. In vitro testing as described in Example 63 yielded the following results, expressed as IC_{50} (nM):

	TLR7	TLR8	TLR9
Experimental	24	29	38
Calculated			78

Example 74

In Vivo Testing

Separate groups of mice are administered 100 μg - 300 μg CpG ODN 2006 (TCGTCGTTTTGTCGTTTTGTCGTT; SEQ ID NO:1) by intraperitoneal injection. One group of mice receiving CpG ODN is also administered 100 ng - 300 μg of a

compound of the invention, orally or intravenously. Serum samples are obtained from mice from each group and/or mice from each group are sacrificed at one or more specified times, 1 to 48 hours following administration of CpG ODN alone or CpG ODN plus compound of the invention. Cytokine expression is evaluated in sera and/or splenocyte cultures derived from each group at each time point. Th1 cytokine expression in mice receiving both CpG ODN and compound of the invention is reduced compared to Th1 cytokine expression in mice receiving CpG ODN alone. Percent of control expression of Th1 cytokine is plotted as a function of concentration of compound of the invention. IC_{50} corresponds to the concentration of compound which reduces Th1 cytokine expression to 50 percent of control expression of Th1 cytokine.

Example 75

In Vivo Testing in a Murine Model of Autoimmune Diabetes Mellitus

Two groups of age-matched female non-obese diabetic (NOD) mice are administered 100 μg - 300 μg CpG ODN 2006 by intraperitoneal injection, once weekly beginning at six weeks of age. One group of NOD mice receiving CpG ODN is also administered 100 ng - 300 μg of a compound of the invention, orally or intravenously, once weekly beginning at six weeks of age. Optionally another group of age-matched female NOD mice receiving compound alone can also be included, as can be another group of age-matched female NOD mice receiving neither CpG ODN nor compound. All mice are maintained on a regular diet and monitored at least once weekly for development of hyperglycemia (random blood glucose ≥ 350 mg/dL measured on at least one occasion). Age at development of hyperglycemia is compared between groups. The group receiving CpG ODN alone develops hyperglycemia earlier than the group receiving CpG ODN and compound.

EQUIVALENTS

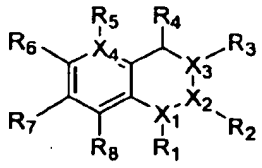
The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by examples provided, since the examples are intended as a single illustration

of one aspect of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. The advantages and objects of the invention are not necessarily encompassed by each embodiment of the invention.

What is claimed is:

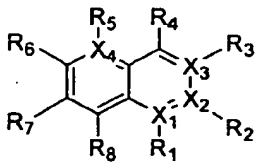
CLAIMS

1. A compound having a structure selected from



(I)

and



(II)

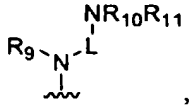
wherein

X_1, X_2, X_3, and X_4 are independently nitrogen or carbon;

R_1 and R_2 are independently absent, hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide;

R_3 is absent, hydrogen, optionally substituted alkyl, optionally substituted alkoxy, halide, Y_1, or Y_3;

R_4 is a group having the structure,



where R_9 is hydrogen or optionally substituted alkyl; L is optionally substituted alkyl; R_{10} and R_{11} are independently hydrogen or optionally substituted alkyl; and together R_{10} and R_{11} can be joined to form an optionally substituted heterocycle, or together R_9 and one of R_{10} or R_{11} can be joined to form an optionally substituted heterocycle;

R_5 is absent or hydrogen;

R_6 and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, halide, Y_1, or Y_2; and

R_8 is hydrogen, optionally substituted alkyl, optionally substituted alkoxy, halide, Y_1, or Y_3;

wherein

Y_1 is Ar-Y_2, where Ar is optionally substituted phenyl;

Y_2 is W-$L_1NR_{12}R_{13}$, where W is O, S, or NR_{14}; L_1 is optionally substituted alkyl; R_{12}, R_{13}, and R_{14} are independently hydrogen or optionally substituted alkyl;

and together R_{12} and R_{13} can be joined to form an optionally substituted heterocycle, or together R_{14} and one of R_{12} or R_{13} can be joined to form an optionally substituted heterocycle;

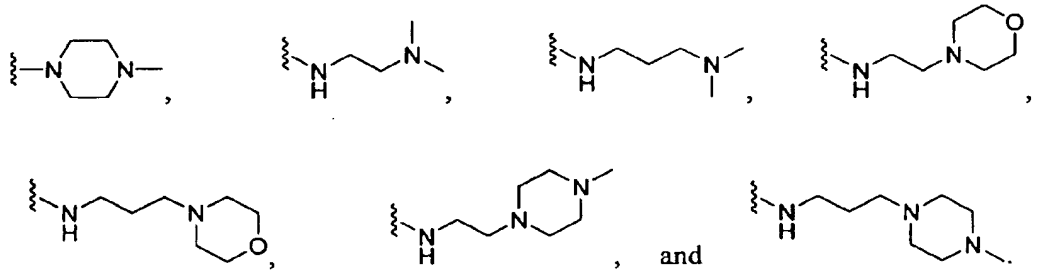
Y_3 is optionally substituted phenyl; and

at least one of R_3, R_6, R_7, and R_8 is Y_1; or at least one of R_6 and R_7 is Y_2; and/or at least one of R_3 and R_8 is Y_3.

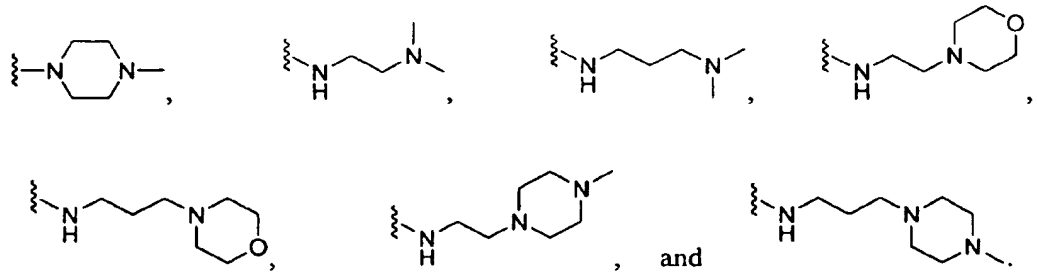
2. A compound as in claim 1, wherein at least one of X_1, X_2, X_3, and X_4 is nitrogen.

3. A compound as in claim 1, wherein at least two of X_1, X_2, X_3, and X_4 are nitrogen.

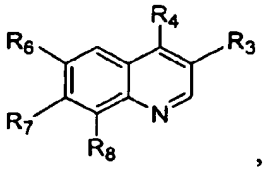
4. A compound as in claim 1, wherein R_4 is selected from



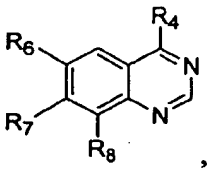
5. A compound as in claim 1, wherein Y_2 is selected from



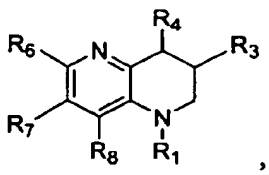
6. A compound as in claim 1, having a structure selelcted from



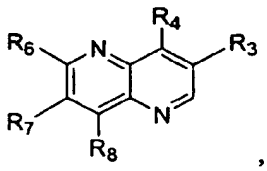
(III)



(IV)

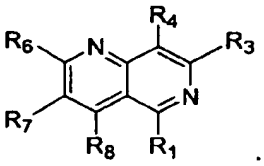


(V)



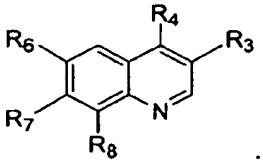
(VI)

and



(VII)

7. A compound as in claim 6, having the structure



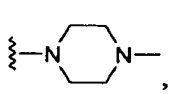
(III)

8. A compound as in claim 7, wherein R_6 is Y_1.

9. A compound as in claim 8, wherein R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

10. A compound as in claim 8, wherein R_3, R_7, and R_8 are hydrogen.

11. A compound as in claim 10, wherein R_4 is selected from



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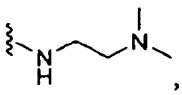

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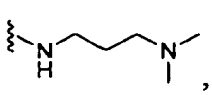

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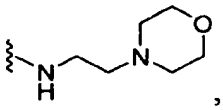

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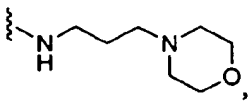

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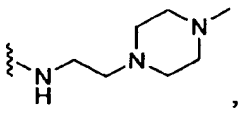

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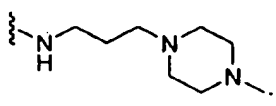

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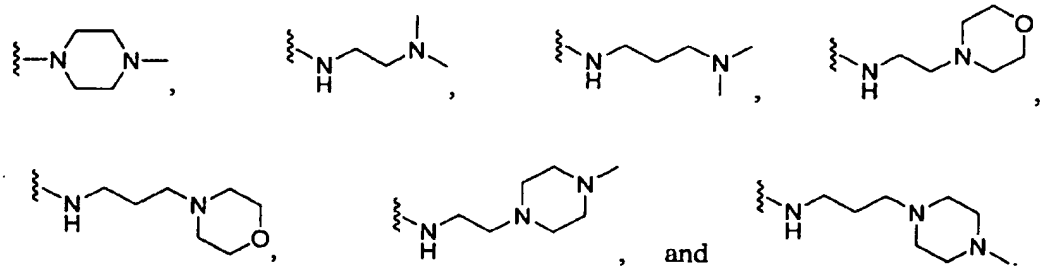
12. A compound as in claim 11, wherein Y_2 is selected from

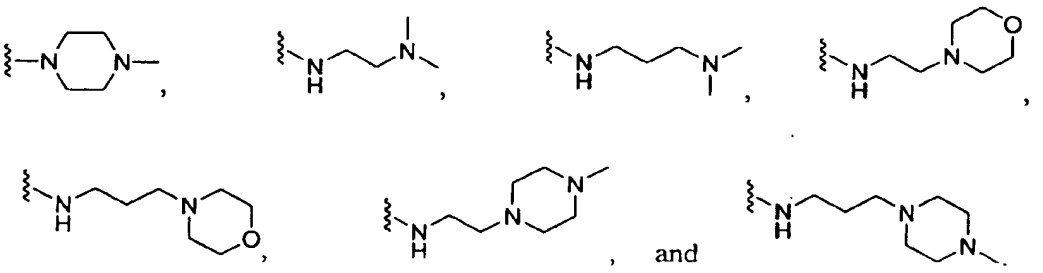


13. A compound as in claim 7, wherein R_7 is Y_1.

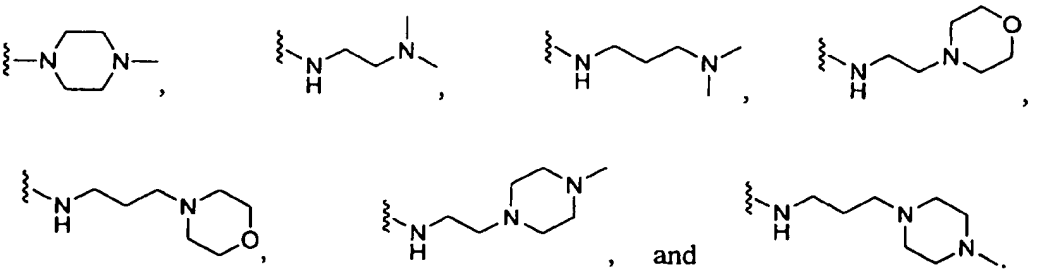
14. A compound as in claim 13, wherein R_3, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

15. A compound as in claim 13, wherein R_3, R_6, and R_8 are hydrogen.

16. A compound as in claim 15, wherein R_4 is selected from



17. A compound as in claim 16, wherein Y_2 is selected from

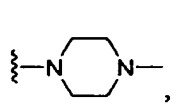
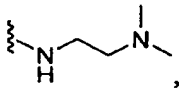
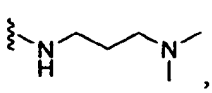
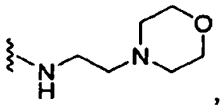


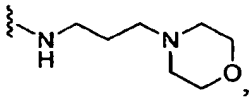
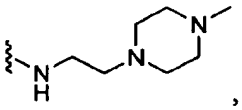
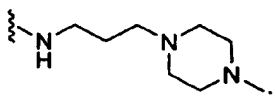
18. A compound as in claim 7, wherein R_8 is Y_1.

19. A compound as in claim 18, wherein R_3, R_6, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

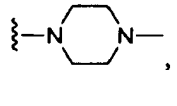
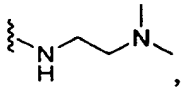
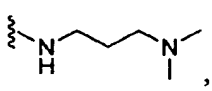
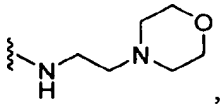
20. A compound as in claim 18, wherein R_3, R_6, and R_7 are hydrogen.

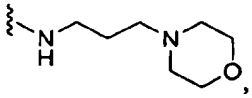
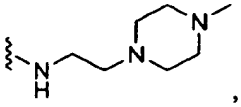
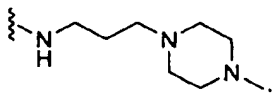
21. A compound as in claim 20, wherein R_4 is selected from

 ,  ,  ,  ,

 ,  , and  .

22. A compound as in claim 21, wherein Y_2 is selected from

 ,  ,  ,  ,

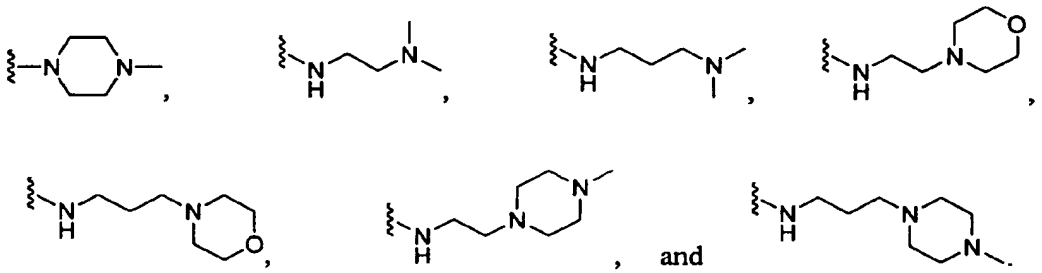
 ,  , and  .

23. A compound as in claim 7, wherein R_3 is Y_1.

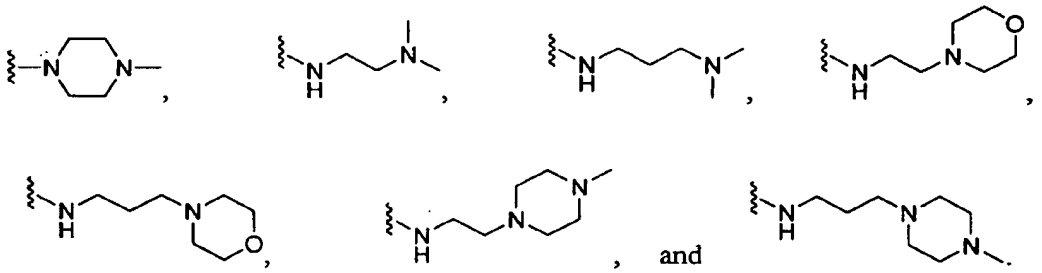
24. A compound as in claim 23, wherein R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

25. A compound as in claim 23, wherein R_6, R_7, and R_8 are hydrogen.

26. A compound as in claim 25, wherein R_4 is selected from



27. A compound as in claim 26, wherein Y_2 is selected from

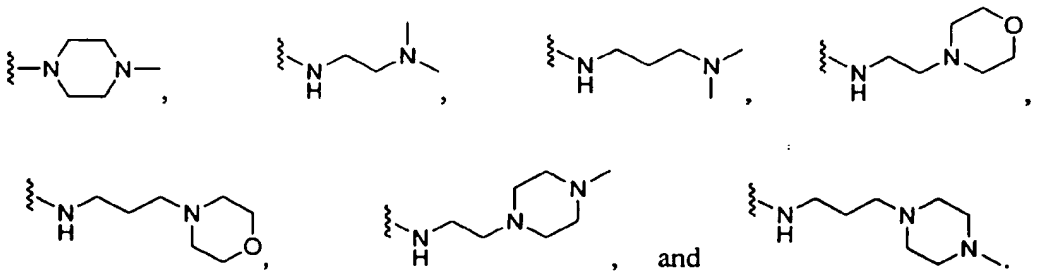


28. A compound as in claim 7, wherein R_6 is Y_2 and R_8 is Y_3.

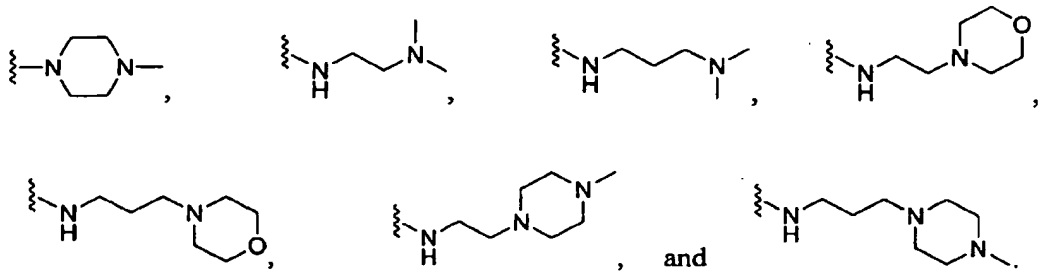
29. A compound as in claim 28, wherein R_3 and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

30. A compound as in claim 28, wherein R_3 and R_7 are hydrogen.

31. A compound as in claim 30, wherein R_4 is selected from



32. A compound as in claim 31, wherein Y_2 is selected from

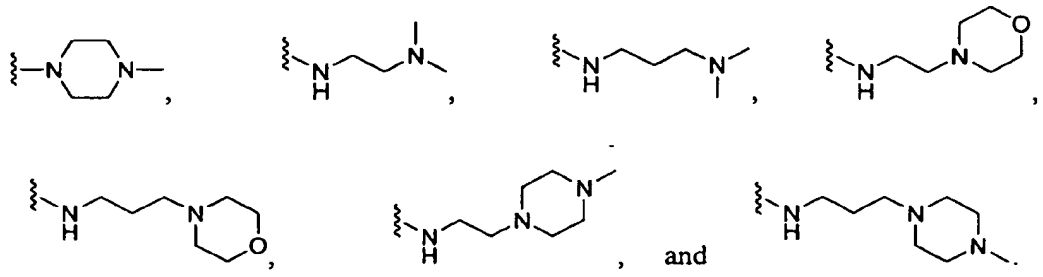


33. A compound as in claim 7, wherein R_3 is Y_3 and R_7 is Y_2.

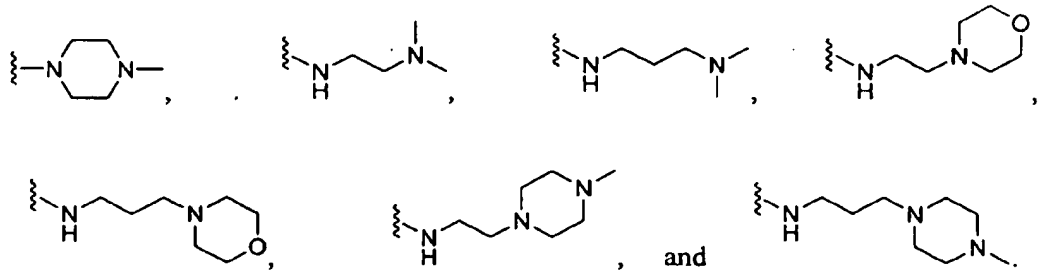
34. A compound as in claim 33, wherein R_6 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

35. A compound as in claim 33, wherein R_6 and R_8 are hydrogen.

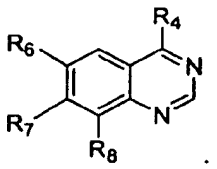
36. A compound as in claim 35, wherein R_4 is selected from



37. A compound as in claim 36, wherein Y_2 is selected from



38. A compound as in claim 1, having the structure



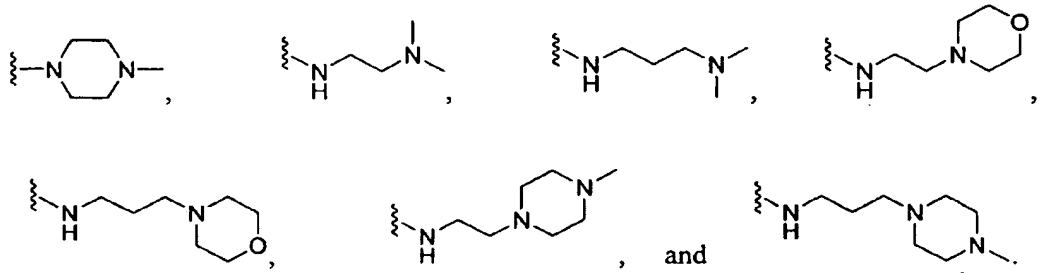
(IV)

39. A compound as in claim 38, wherein R_6 is Y_1.

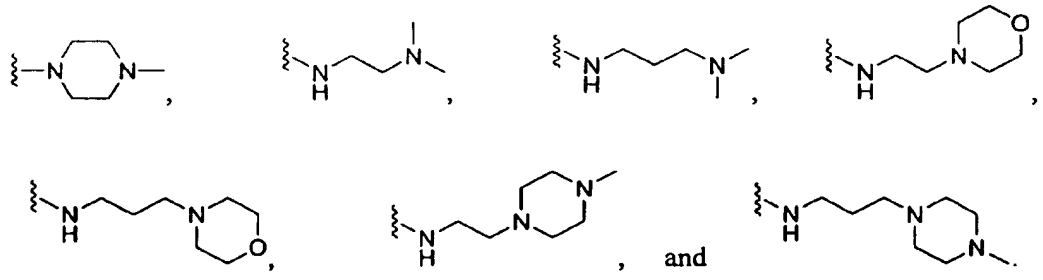
40. A compound as in claim 39, wherein R_7 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

41. A compound as in claim 39, wherein R_7 and R_8 are hydrogen.

42. A compound as in claim 41, wherein R_4 is selected from



43. A compound as in claim 42, wherein Y_2 is selected from

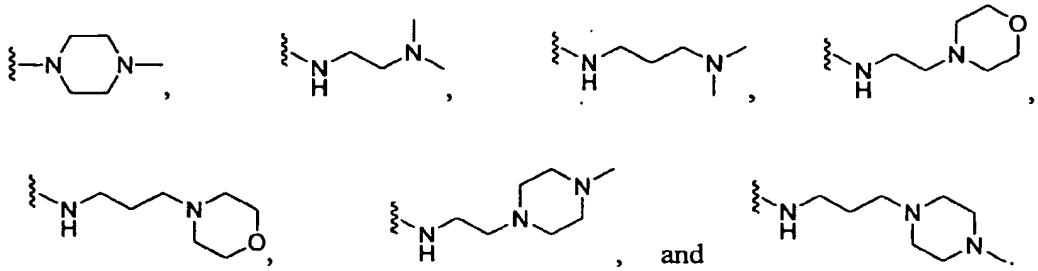


44. A compound as in claim 38, wherein R_7 is Y_1.

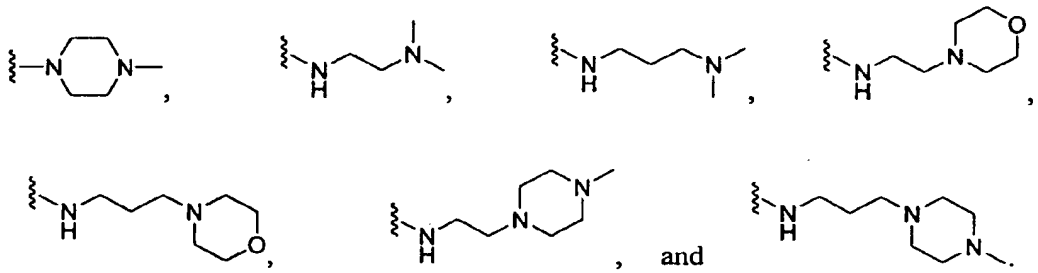
45. A compound as in claim 44, wherein R_6 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

46. A compound as in claim 44, wherein R_6 and R_8 are hydrogen.

47. A compound as in claim 46, wherein R_4 is selected from



48. A compound as in claim 47, wherein Y_2 is selected from

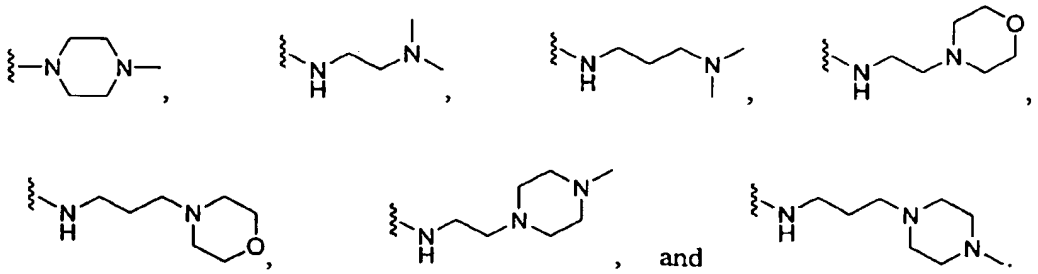


49. A compound as in claim 38, wherein R_8 is Y_1.

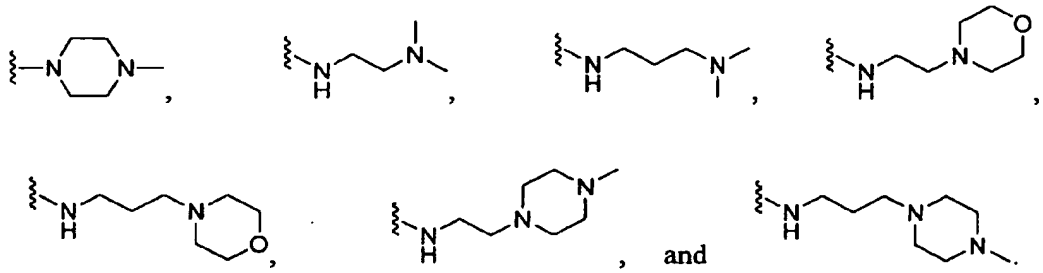
50. A compound as in claim 49, wherein R_6 and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

51. A compound as in claim 49, wherein R_6 and R_7 are hydrogen.

52. A compound as in claim 51, wherein R_4 is selected from



53. A compound as in claim 52, wherein Y_2 is selected from

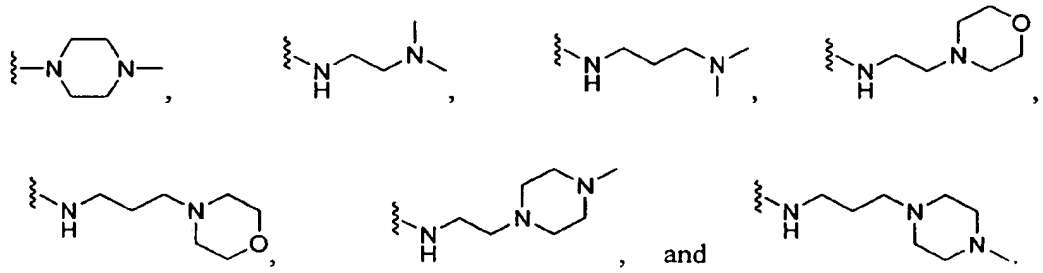


54. A compound as in claim 38, wherein R_6 is Y_2 and R_8 is Y_3.

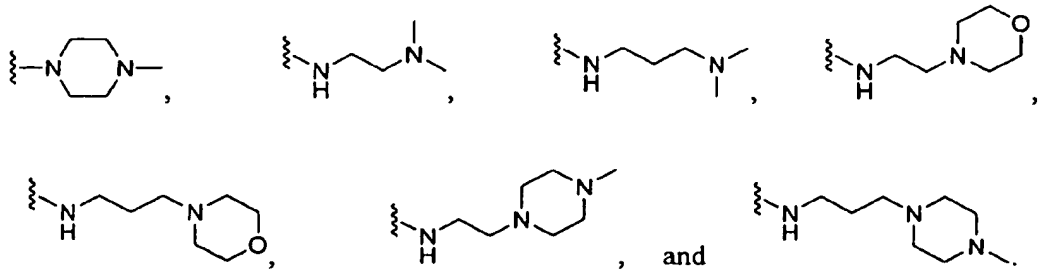
55. A compound as in claim 54, wherein R_7 is hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

56. A compound as in claim 54, wherein R_7 is hydrogen.

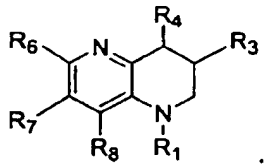
57. A compound as in claim 56, wherein R_4 is selected from



58. A compound as in claim 57, wherein Y_2 is selected from



59. A compound as in claim 6, having the structure



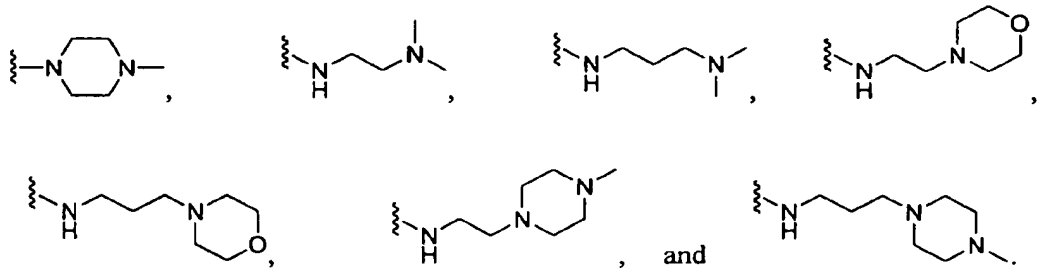
(V)

60. A compound as in claim 59, wherein R_1 is hydrogen and R_6 is Y_1.

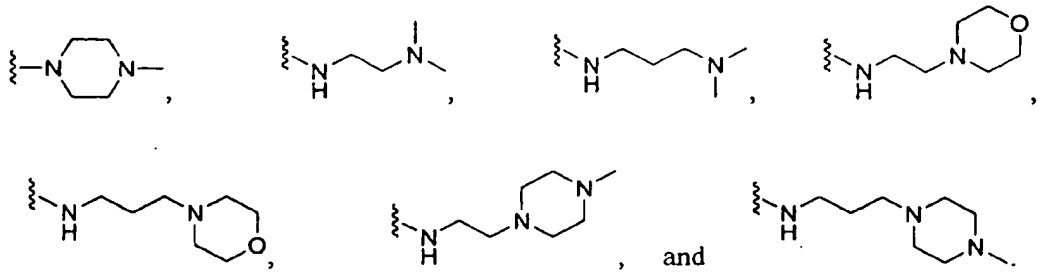
61 A compound as in claim 60, wherein R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

62. A compound as in claim 60, wherein R_3, R_7, and R_8 are hydrogen.

63. A compound as in claim 62, wherein R_4 is selected from



64. A compound as in claim 63, wherein Y_2 is selected from

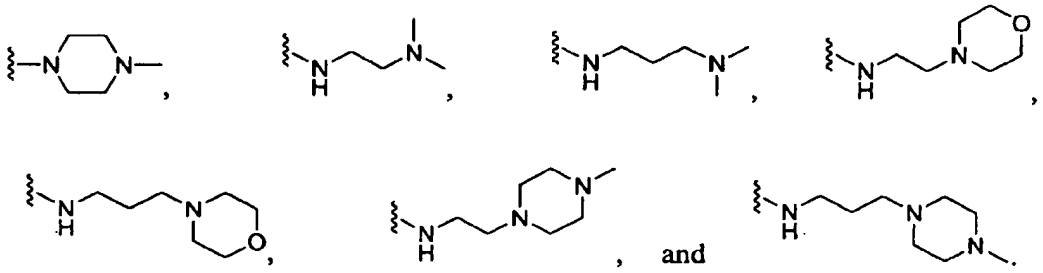


65. A compound as in claim 59, wherein R_1 is hydrogen and R_7 is Y_1.

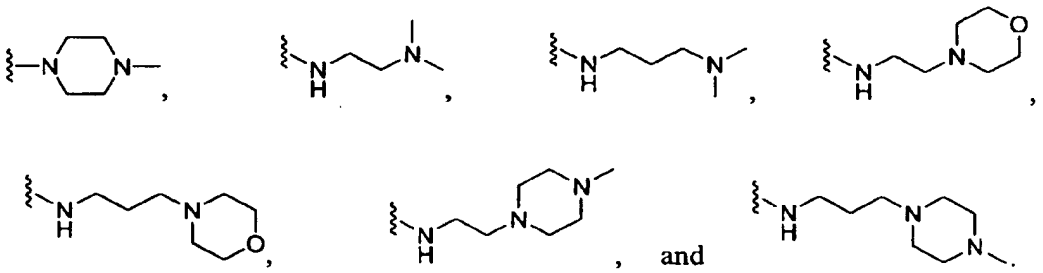
66. A compound as in claim 65, wherein R_3, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

67. A compound as in claim 65, wherein R_3, R_6, and R_8 are hydrogen.

68. A compound as in claim 67, wherein R_4 is selected from



69. A compound as in claim 68, wherein Y_2 is selected from

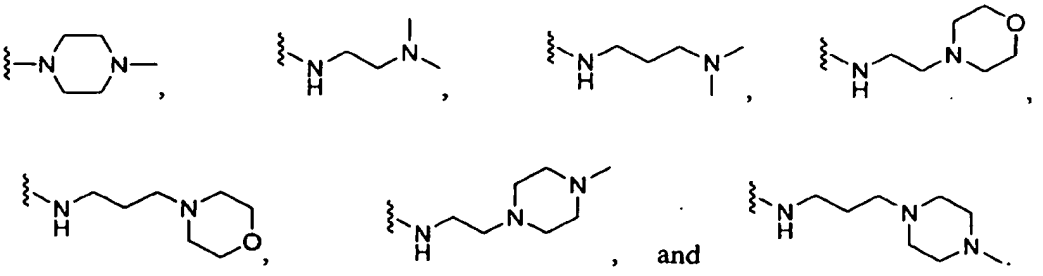


70. A compound as in claim 59, wherein R_1 is hydrogen and R_8 is Y_1.

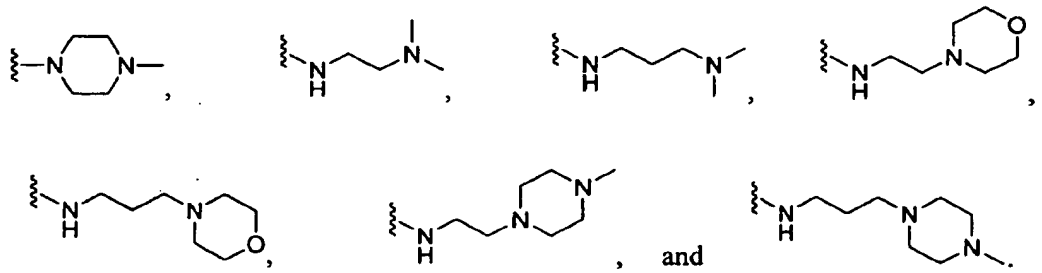
71. A compound as in claim 70, wherein R_3, R_6, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

72. A compound as in claim 70, wherein R_3, R_6, and R_7 are hydrogen.

73. A compound as in claim 72, wherein R_4 is selected from



74. A compound as in claim 73, wherein Y_2 is selected from

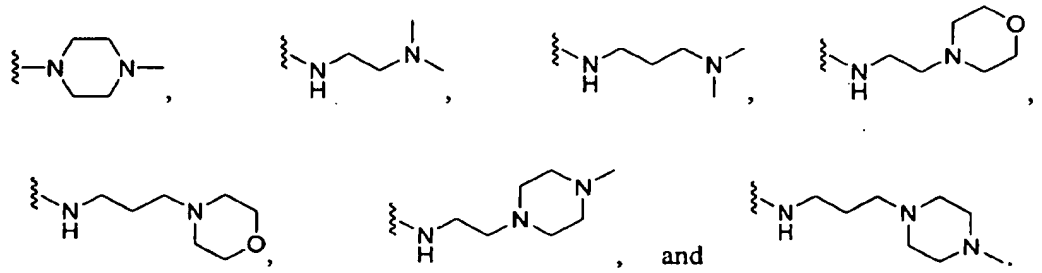


75. A compound as in claim 59, wherein R_1 is hydrogen and R_3 is Y_1.

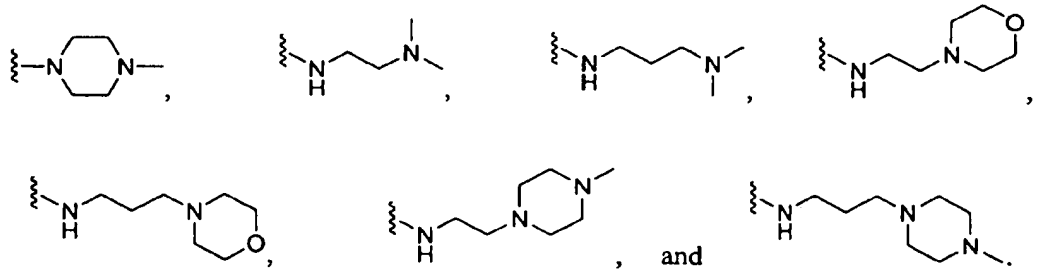
76. A compound as in claim 75, wherein R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

77. A compound as in claim 75, wherein R_6, R_7, and R_8 are hydrogen.

78. A compound as in claim 77, wherein R_4 is selected from



79. A compound as in claim 78, wherein Y_2 is selected from

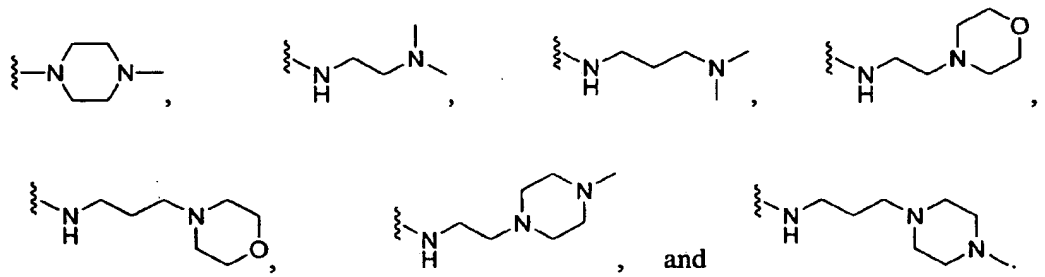


80. A compound as in claim 59, wherein R_1 is hydrogen, R_6 is Y_2, and R_8 is Y_3.

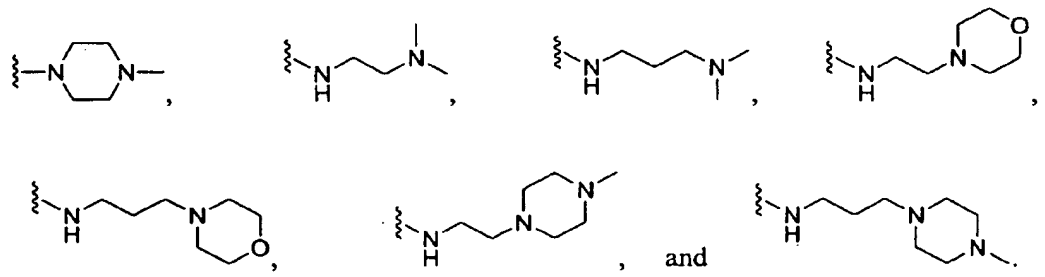
81. A compound as in claim 80, wherein R_3 and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

82. A compound as in claim 80, wherein R_3 and R_7 are hydrogen.

83. A compound as in claim 82, wherein R_4 is selected from



84. A compound as in claim 83, wherein Y_2 is selected from

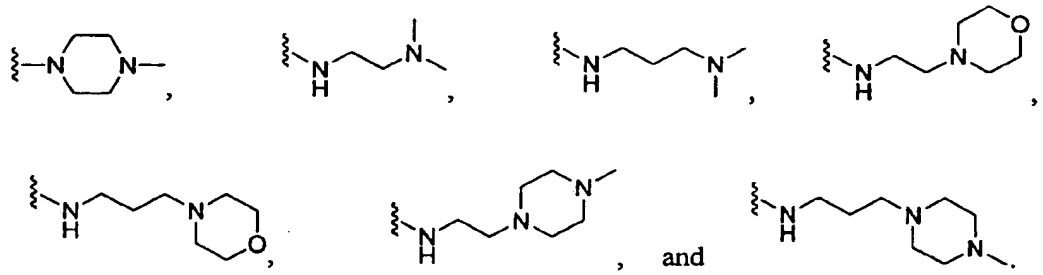


85. A compound as in claim 59, wherein R_1 is hydrogen, R_3 is Y_3, and R_7 is Y_2.

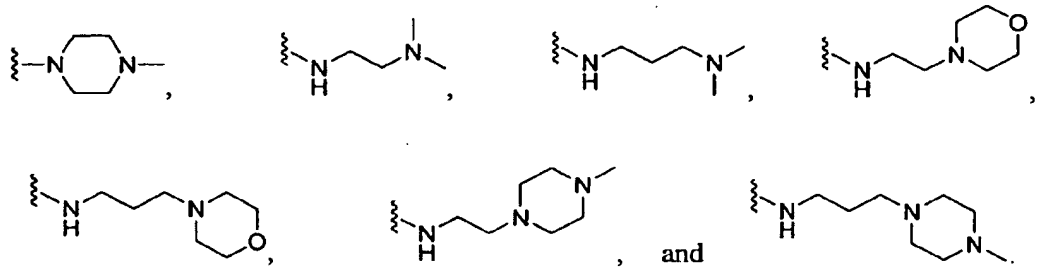
86. A compound as in claim 85, wherein R_6 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

87. A compound as in claim 85, wherein R_6 and R_8 are hydrogen.

88. A compound as in claim 87, wherein R_4 is selected from



89. A compound as in claim 88, wherein Y_2 is selected from

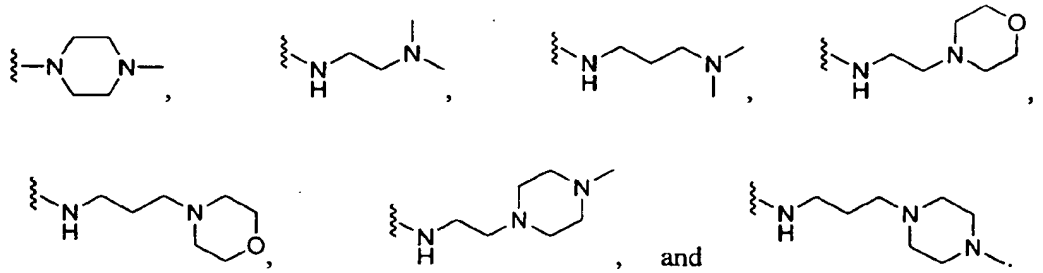


90. A compound as in claim 59, wherein R_1 is Y_3 and R_7 is Y_2.

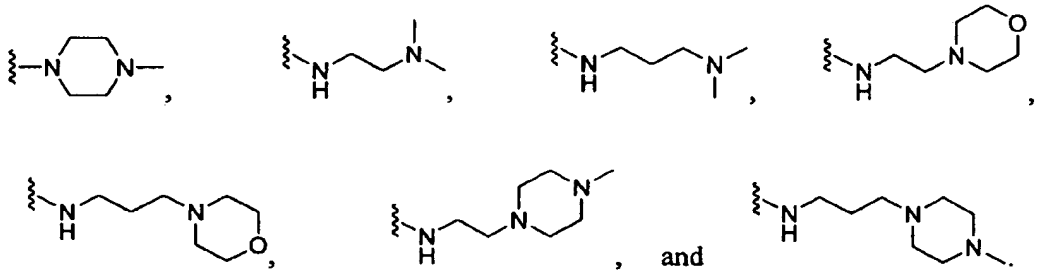
91. A compound as in claim 90, wherein R_3, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

92. A compound as in claim 90, wherein R_3, R_6, R_7, and R_8 are hydrogen.

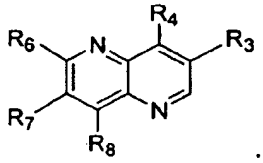
93. A compound as in claim 92, wherein R_4 is selected from



94. A compound as in claim 93, wherein Y_2 is selected from



95. A compound as in claim 6, having the structure



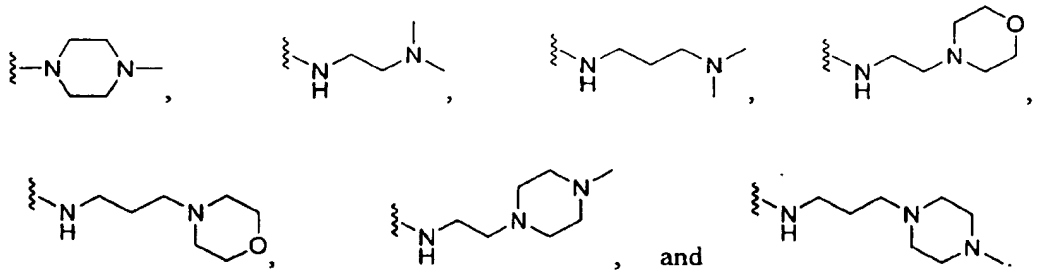
(VI)

96. A compound as in claim 95, wherein R_6 is Y_1.

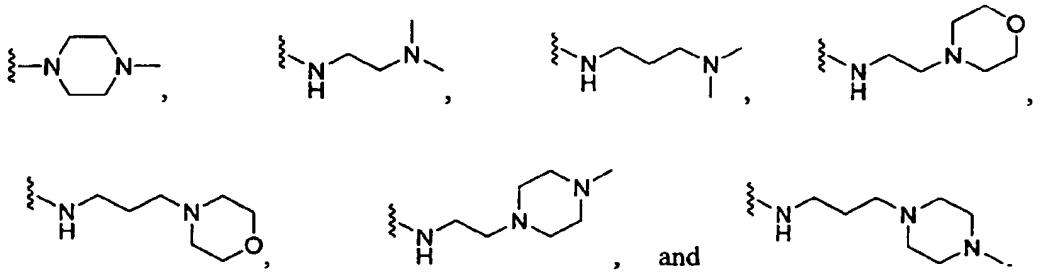
97. A compound as in claim 96, wherein R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

98. A compound as in claim 96, wherein R_3, R_7, and R_8 are hydrogen.

99. A compound as in claim 98, wherein R_4 is selected from



100. A compound as in claim 99, wherein Y_2 is selected from

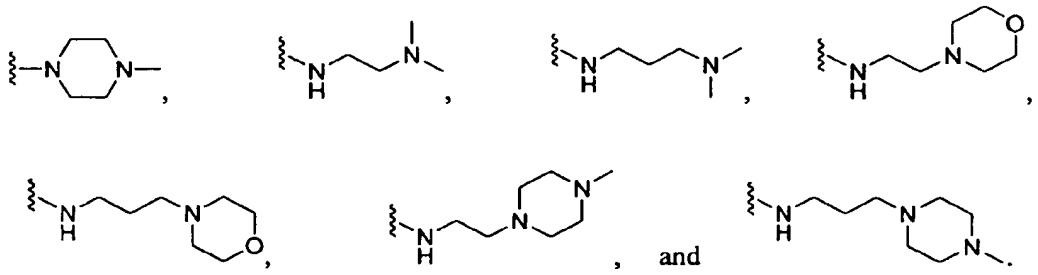


101. A compound as in claim 95, wherein R_7 is Y_1.

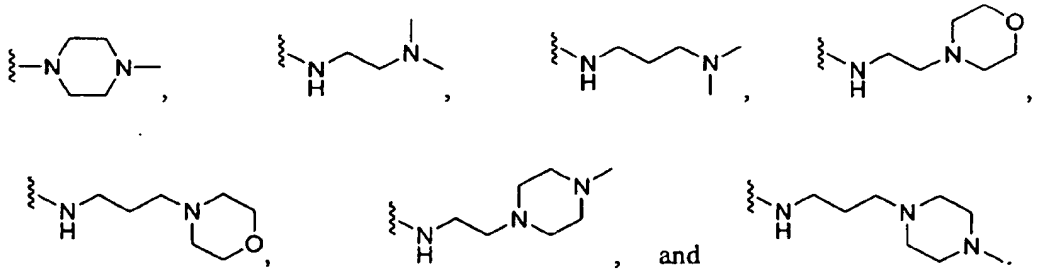
102. A compound as in claim 101, wherein R_3, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

103. A compound as in claim 101, wherein R_3, R_6, and R_8 are hydrogen.

104. A compound as in claim 103, wherein R_4 is selected from



105. A compound as in claim 104, wherein Y_2 is selected from

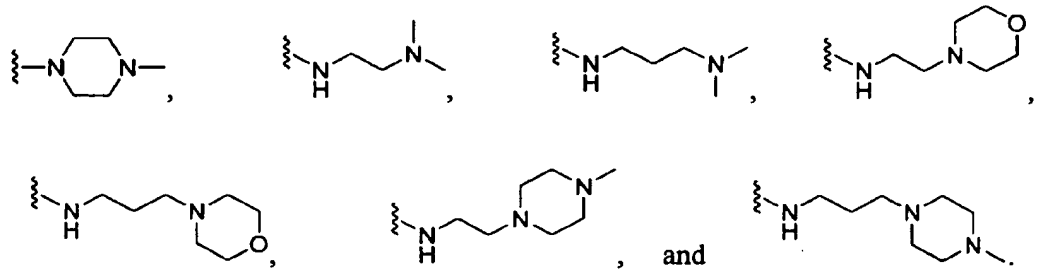


106. A compound as in claim 95, wherein R_8 is Y_1.

107. A compound as in claim 106, wherein R_3, R_6, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

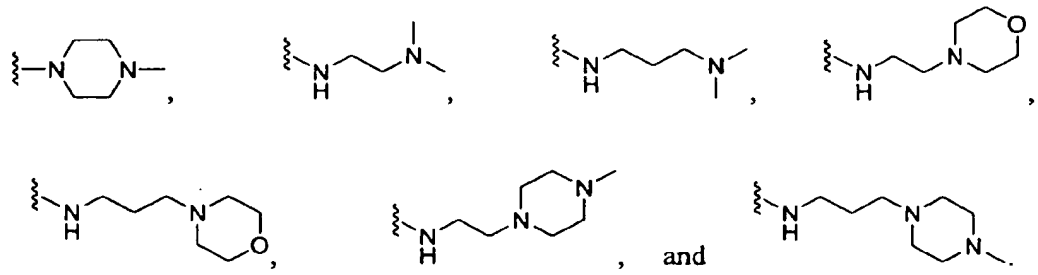
108. A compound as in claim 106, wherein R_3, R_6, and R_7 are hydrogen.

109. A compound as in claim 108, wherein R_4 is selected from



and

110. A compound as in claim 109, wherein Y_2 is selected from



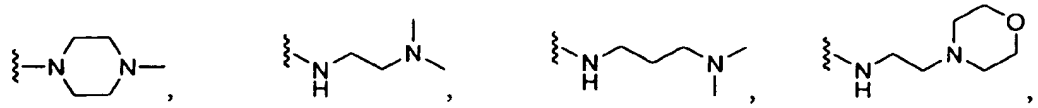
and

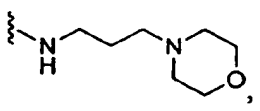
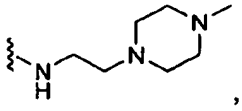
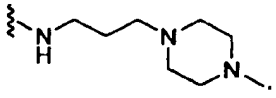
111. A compound as in claim 95, wherein R_3 is Y_1.

112. A compound as in claim 111, wherein R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

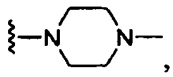
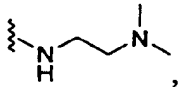
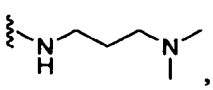
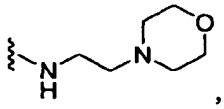
113. A compound as in claim 111, wherein R_6, R_7, and R_8 are hydrogen.

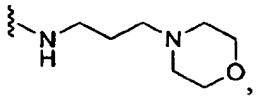
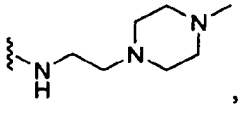
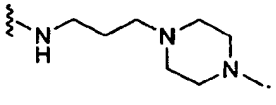
114. A compound as in claim 113, wherein R_4 is selected from





and


115. A compound as in claim 114, wherein Y_2 is selected from

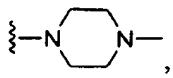
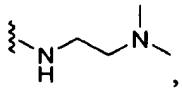
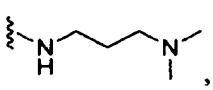
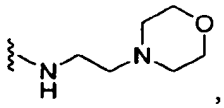


and


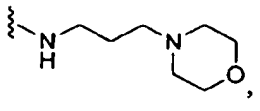
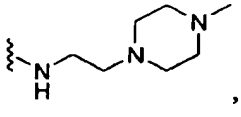
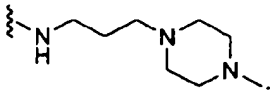
116. A compound as in claim 95, wherein R_6 is Y_2 and R_8 is Y_3.

117. A compound as in claim 116, wherein R_3 and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

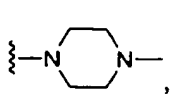
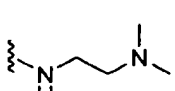
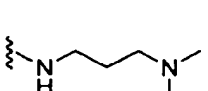
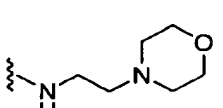
118. A compound as in claim 116, wherein R_3 and R_7 are hydrogen.

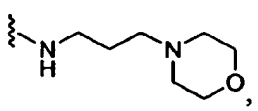
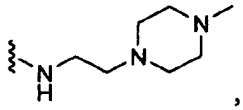
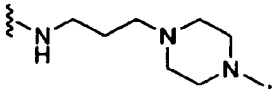
119. A compound as in claim 118, wherein R_4 is selected from



and


120. A compound as in claim 119, wherein Y_2 is selected from

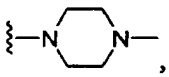
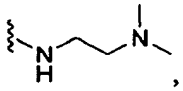
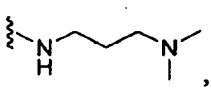
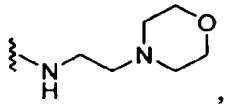
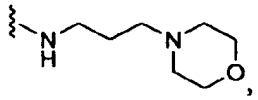
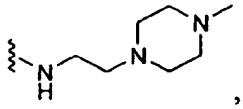


and


121. A compound as in claim 95, wherein R_3 is Y_3 and R_7 is Y_2.

122. A compound as in claim 121, wherein R_6 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

123. A compound as in claim 121, wherein R_6 and R_8 are hydrogen.

124. A compound as in claim 123, wherein R_4 is selected from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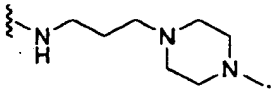
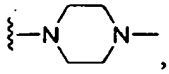
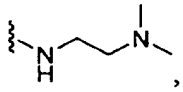
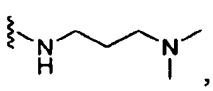
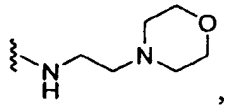
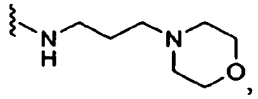
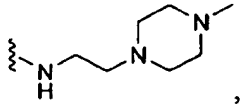
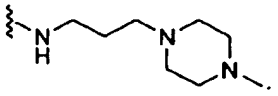
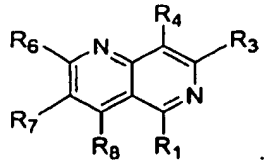


125. A compound as in claim 124, wherein Y_2 is selected from







and


126. A compound as in claim 6, having the structure



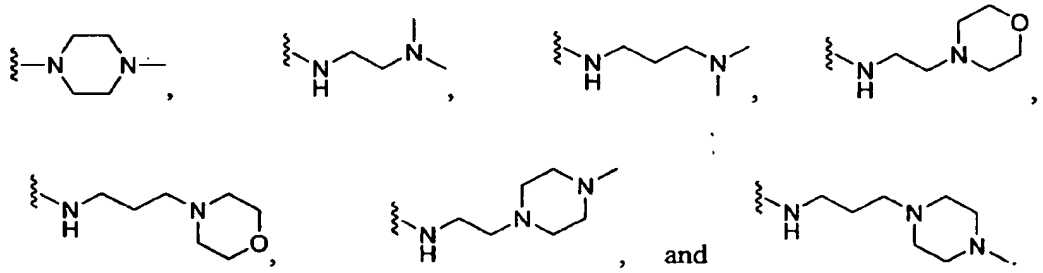
(VII)

127. A compound as in claim 126, wherein R_6 is Y_1.

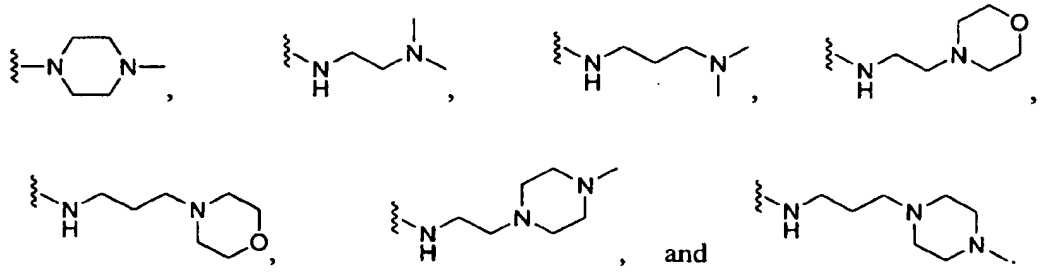
128. A compound as in claim 127, wherein R_1, R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

129. A compound as in claim 127, wherein R_1, R_3, R_7, and R_8 are hydrogen.

130. A compound as in claim 129, wherein R_4 is selected from



131. A compound as in claim 130, wherein Y_2 is selected from

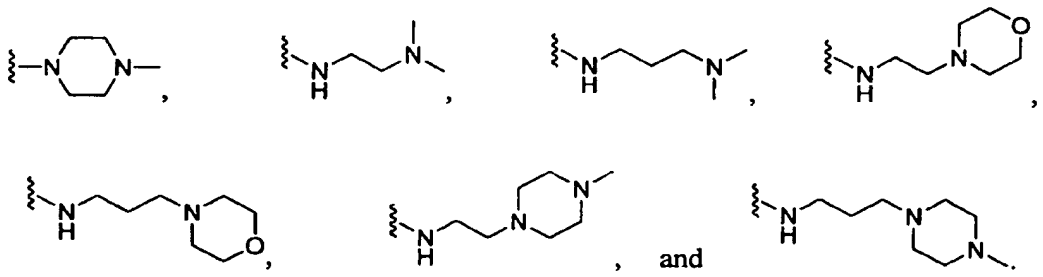


132. A compound as in claim 126, wherein R_7 is Y_1.

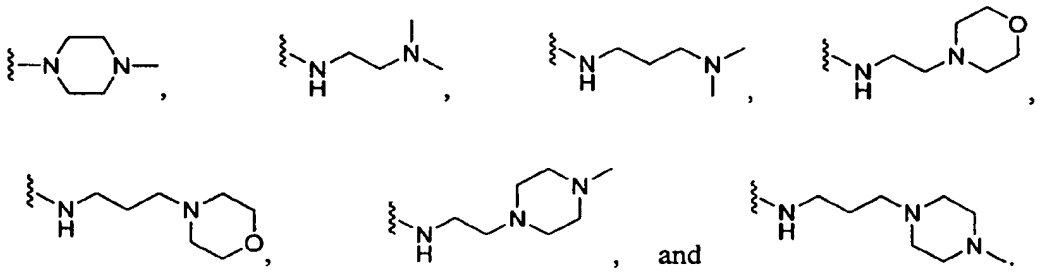
133. A compound as in claim 132, wherein R_1, R_3, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

134. A compound as in claim 132, wherein R_1, R_3, R_6, and R_8 are hydrogen.

135. A compound as in claim 134, wherein R_4 is selected from



136. A compound as in claim 135, wherein Y_2 is selected from

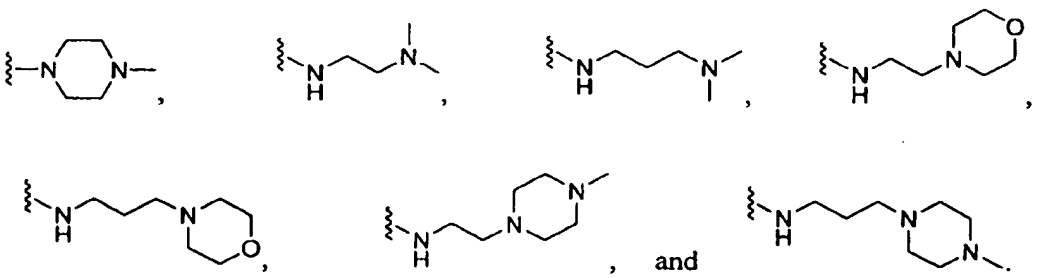


137. A compound as in claim 126, wherein R_8 is Y_1.

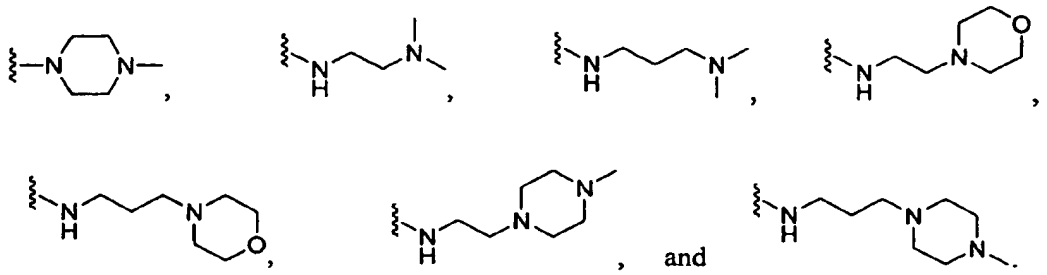
138. A compound as in claim 137, wherein R_1, R_3, R_6, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

139. A compound as in claim 137, wherein R_1, R_3, R_6, and R_7 are hydrogen.

140. A compound as in claim 139, wherein R_4 is selected from



141. A compound as in claim 140, wherein Y_2 is selected from

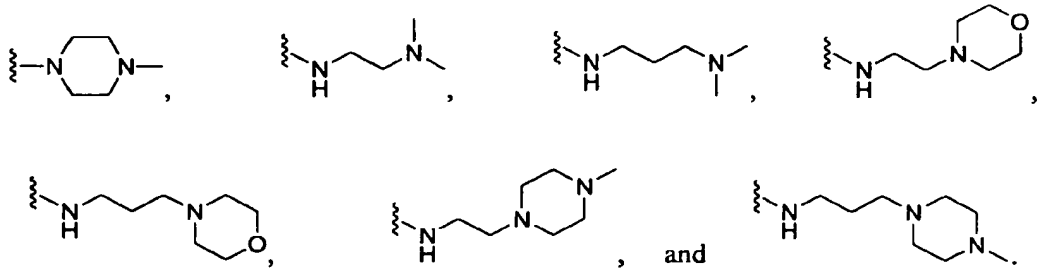


142. A compound as in claim 126, wherein R_3 is Y_1.

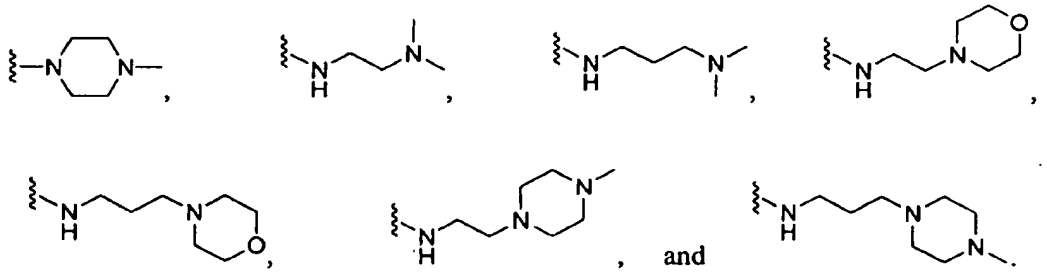
143. A compound as in claim 142, wherein R_1, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

144. A compound as in claim 142, wherein R_1, R_6, R_7, and R_8 are hydrogen.

145. A compound as in claim 144, wherein R_4 is selected from



146. A compound as in claim 145, wherein Y_2 is selected from

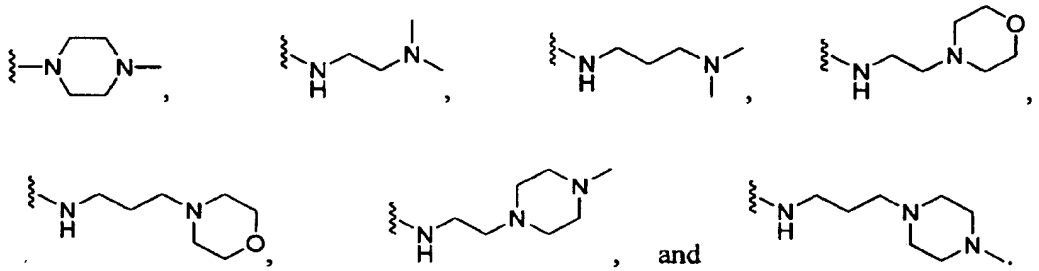


147. A compound as in claim 126, wherein R_6 is Y_2 and R_8 is Y_3.

148. A compound as in claim 147, wherein R_1, R_3, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

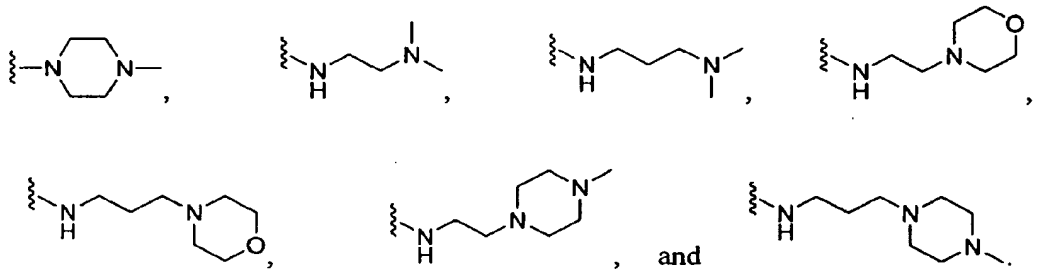
149. A compound as in claim 147, wherein R_1, R_3, and R_7 are hydrogen.

150. A compound as in claim 149, wherein R_4 is selected from



and

151. A compound as in claim 150, wherein Y_2 is selected from



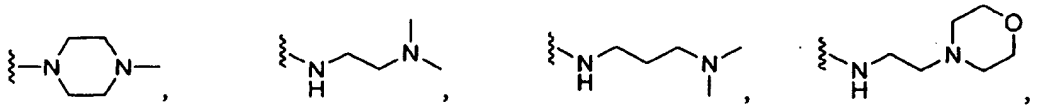
and

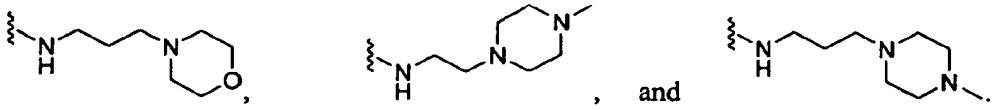
152. A compound as in claim 126, wherein R_3 is Y_3 and R_7 is Y_2.

153. A compound as in claim 152, wherein R_1, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

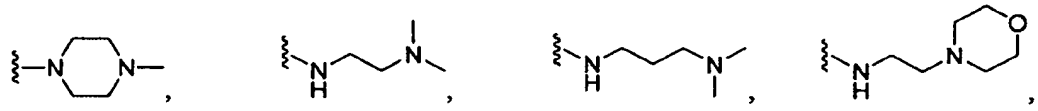
154. A compound as in claim 152, wherein R_1, R_6, and R_8 are hydrogen.

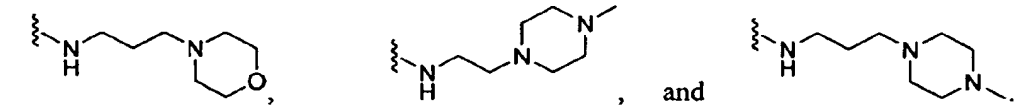
155. A compound as in claim 154, wherein R_4 is selected from



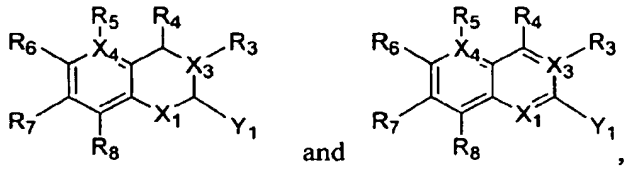


156. A compound as in claim 155, wherein Y_2 is selected from





157. A compound having a structure selected from



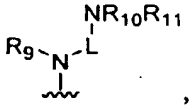
(VIII) and (IX),

wherein

X_1, X_3, and X_4 are independently nitrogen or carbon;

R_3 is absent, hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide;

R_4 is a group having the structure,



where R_9 is hydrogen or optionally substituted alkyl; L is optionally substituted alkyl; R_{10} and R_{11} are independently hydrogen or optionally substituted alkyl; and together R_{10} and R_{11} can be joined to form an optionally substituted heterocycle, or together R_9 and one of R_{10} or R_{11} can be joined to form an optionally substituted heterocycle;

R_5 is absent, hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide;

R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide; and

Y_1 is Ar-Y_2, where Ar is optionally substituted phenyl;

wherein

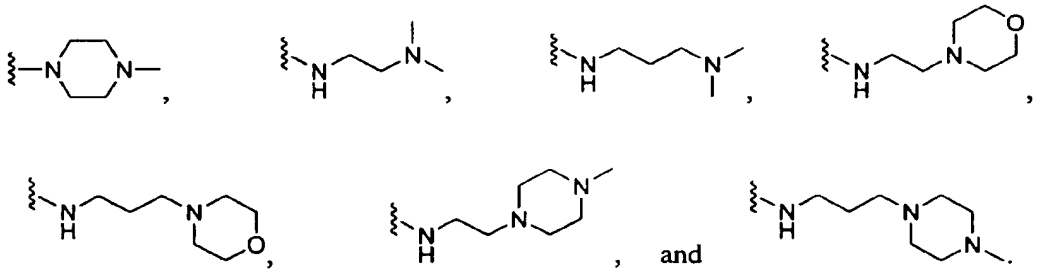
Y_2 is W-$L_1NR_{12}R_{13}$, where W is O, S, or NR_{14}; L_1 is optionally substituted alkyl; R_{12}, R_{13}, and R_{14} are independently hydrogen or optionally substituted alkyl; and together R_{12} and R_{13} can be joined to form an optionally substituted heterocycle, or together R_{14} and one of R_{12} or R_{13} can be joined to form an optionally substituted heterocycle;

wherein, when the compound has the structure (IX) wherein X_3 is nitrogen, X_4 is nitrogen.

158. A compound as in claim 157, wherein at least one of X_1, X_3, and X_4 is nitrogen.

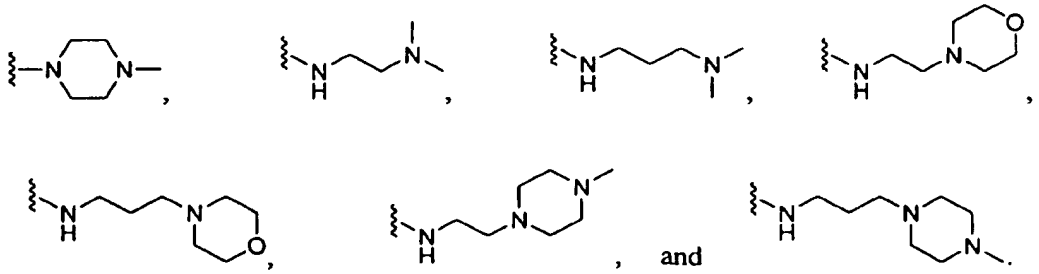
159. A compound as in claim 157, wherein at least two of X_1, X_3, and X_4 are nitrogen.

160. A compound as in claim 157, wherein R_4 is selected from



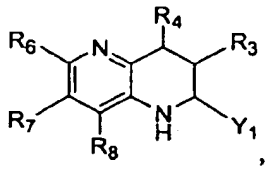
and

161. A compound as in claim 157, wherein Y_2 is selected from



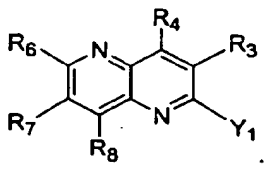
and

162. A compound as in claim 157, having a structure selected from



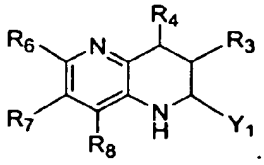
(X)

and



(XI)

163. A compound as in claim 162, having the structure

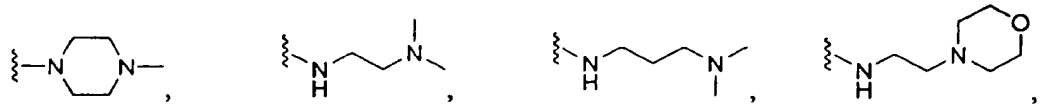


(X)

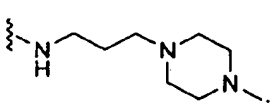
164. A compound as in claim 163, wherein R_3, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

165. A compound as in claim 163, wherein R_3, R_6, R_7, and R_8 are hydrogen.

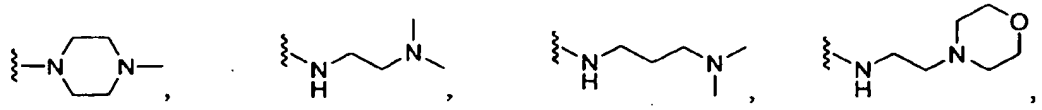
166. A compound as in claim 165, wherein R_4 is selected from

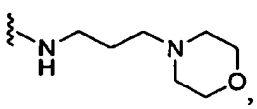
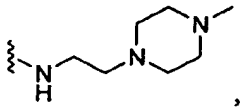
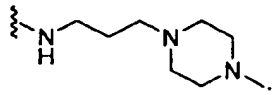


and

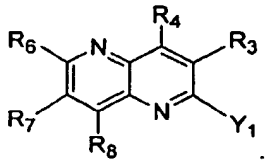


167. A compound as in claim 166, wherein Y_2 is selected from





and


168. A compound as in claim 162, having the structure

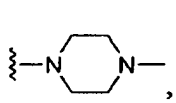
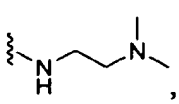
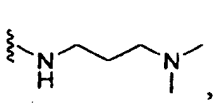
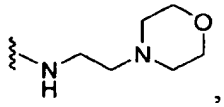
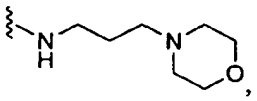
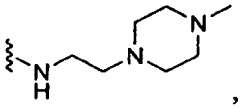
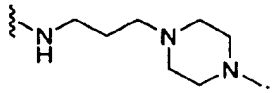


(XI)

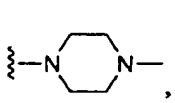
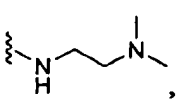
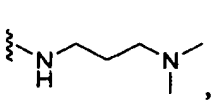
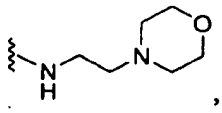
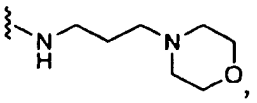
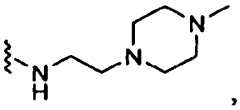
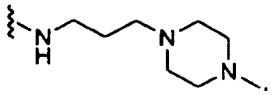
169. A compound as in claim 168, wherein R_3, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

170. A compound as in claim 168, wherein R_3, R_6, R_7, and R_8 are hydrogen.

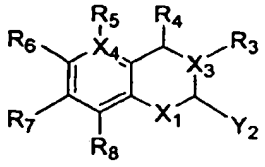
171. A compound as in claim 170, wherein R_4 is selected from







and


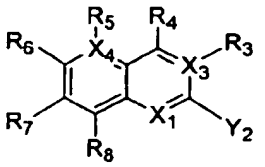
172. A compound as in claim 171, wherein Y_2 is selected from







and


173. A compound having a structure selected from



and



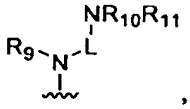
(XII) (XIII)

wherein

X_1, X_3, and X_4 are independently nitrogen or carbon;

R_3 is absent, hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide;

R_4 is a group having the structure,



where R_9 is hydrogen or optionally substituted alkyl; L is optionally substituted alkyl; R_{10} and R_{11} are independently hydrogen or optionally substituted alkyl; and together R_{10} and R_{11} can be joined to form an optionally substituted heterocycle, or together R_9 and one of R_{10} or R_{11} can be joined to form an optionally substituted heterocycle;

R_5 is absent or hydrogen;

R_6 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, halide, or Y_3;

R_7 is hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide; and

Y_2 is W-$L_1NR_{12}R_{13}$, where W is O, S, or NR_{14}; L_1 is optionally substituted alkyl; R_{12}, R_{13}, and R_{14} are independently hydrogen or optionally substituted alkyl; and together R_{12} and R_{13} can be joined to form an optionally substituted heterocycle, or together R_{14} and one of R_{12} or R_{13} can be joined to form an optionally substituted heterocycle;

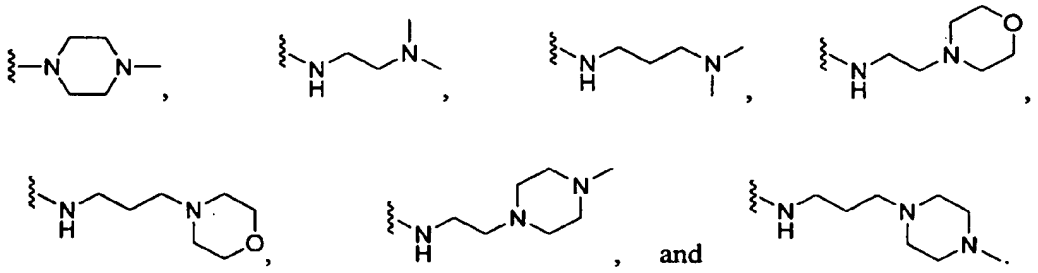
wherein

Y_3 is optionally substituted phenyl.

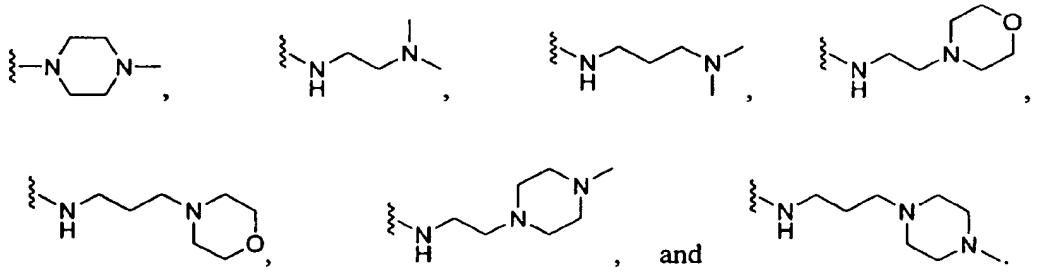
174. A compound as in claim 173, wherein at least one of X_1, X_3, and X_4 is nitrogen.

175. A compound as in claim 173, wherein at least two of X_1, X_3, and X_4 are nitrogen.

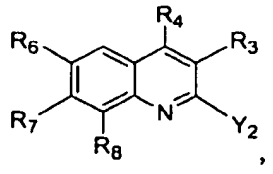
176. A compound as in claim 173, wherein R_4 is selected from



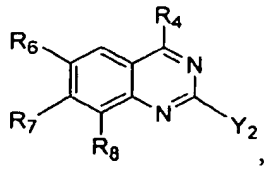
177. A compound as in claim 173, wherein Y_2 is selected from



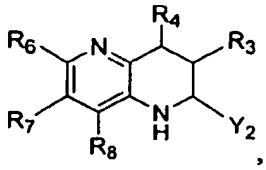
178. A compound as in claim 173, having a structure selected from



(XIV)

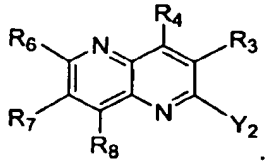


(XV)



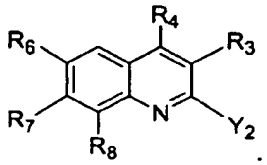
(XVI)

and



(XVII)

179. A compound as in claim 178, having the structure



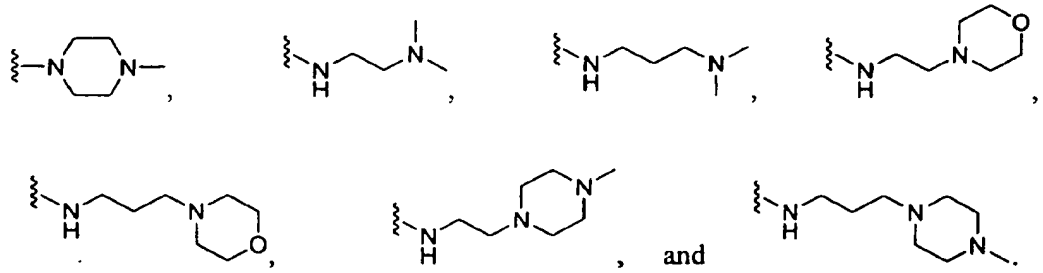
(XIV)

180. A compound as in claim 179, wherein R_6 is Y_3.

181. A compound as in claim 180, wherein R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

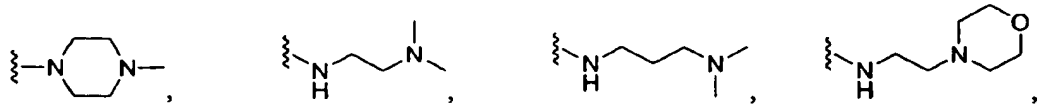
182. A compound as in claim 180, wherein R_3, R_7, and R_8 are hydrogen.

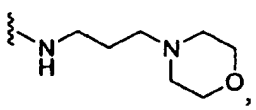
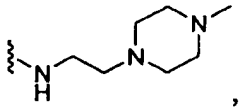
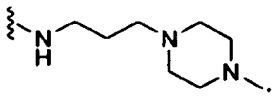
183. A compound as in claim 182, wherein R_4 is selected from



and

184. A compound as in claim 183, wherein Y_2 is selected from



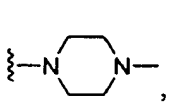
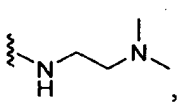
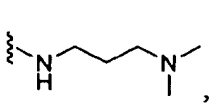
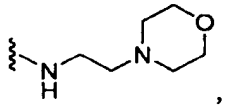
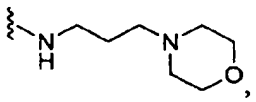
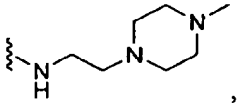
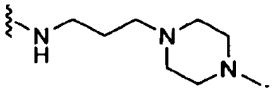


and


185. A compound as in claim 179, wherein R_8 is Y_3.

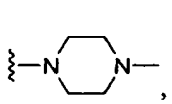
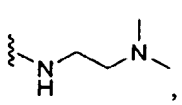
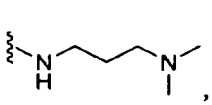
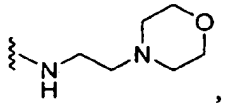
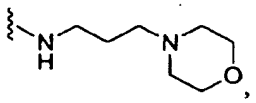
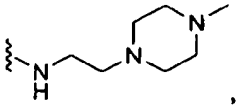
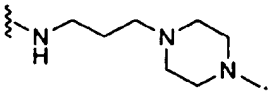
186. A compound as in claim 185, wherein R_3, R_6, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

187. A compound as in claim 185, wherein R_3, R_6, and R_7 are hydrogen.

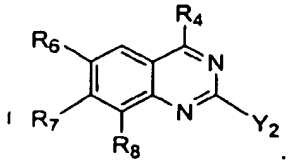
188. A compound as in claim 187, wherein R_4 is selected from







and


189. A compound as in claim 188, wherein Y_2 is selected from







and


190. A compound as in claim 178, having the structure



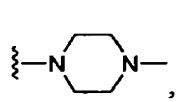
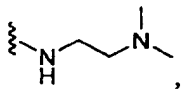
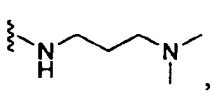
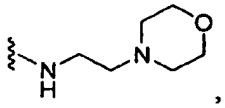
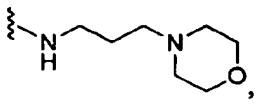
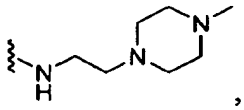
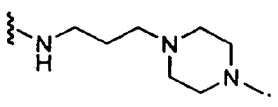
(XV)

191. A compound as in claim 190, wherein R_6 is Y_3.

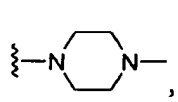
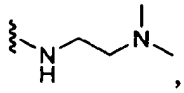
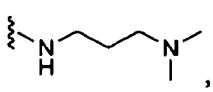
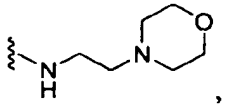
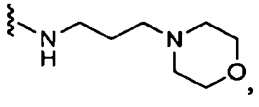
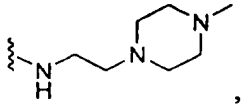
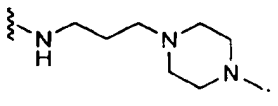
192. A compound as in claim 191, wherein R_7 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

193. A compound as in claim 191, wherein R_7 and R_8 are hydrogen.

194. A compound as in claim 193, wherein R_4 is selected from







and


195. A compound as in claim 194, wherein Y_2 is selected from

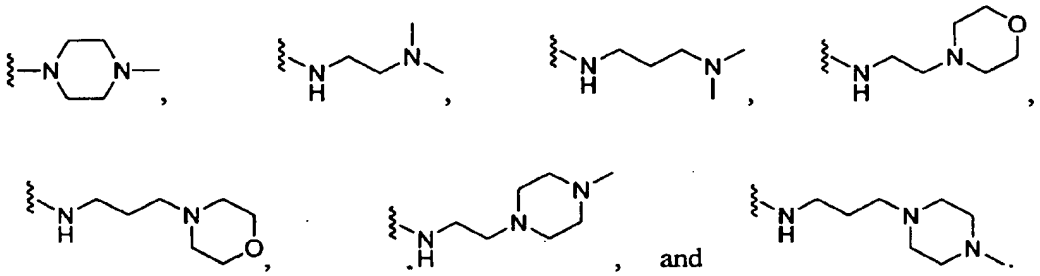






and


196. A compound as in claim 190, wherein R_8 is Y_3.

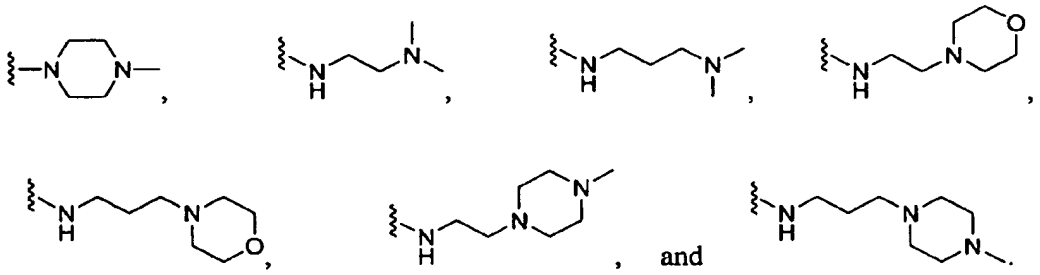
197. A compound as in claim 196, wherein R_6 and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

198. A compound as in claim 196, wherein R_6 and R_7 are hydrogen.

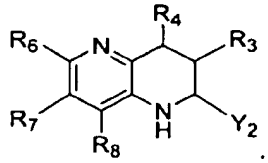
199. A compound as in claim 198, wherein R_4 is selected from



200. A compound as in claim 199, wherein Y_2 is selected from



201. A compound as in claim 178, having the structure



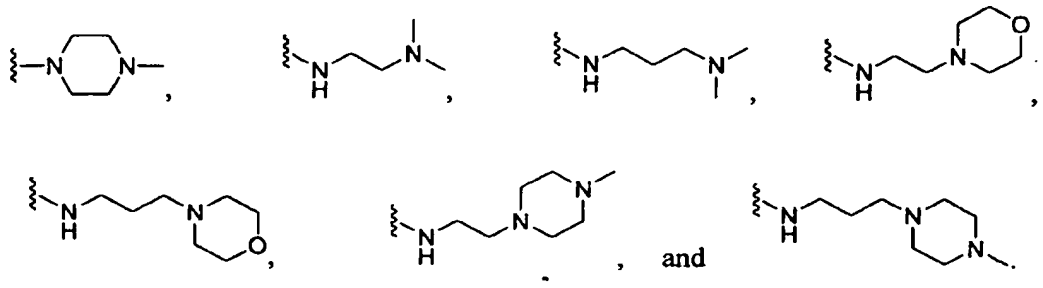
(XVI)

202. A compound as in claim 201, wherein R_6 is Y_3.

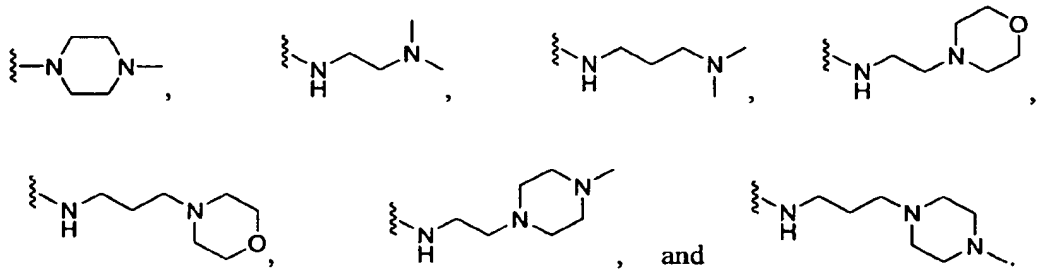
203. A compound as in claim 202, wherein R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

204. A compound as in claim 202, wherein R_3, R_7, and R_8 are hydrogen.

205. A compound as in claim 204, wherein R_4 is selected from



206. A compound as in claim 205, wherein Y_2 is selected from

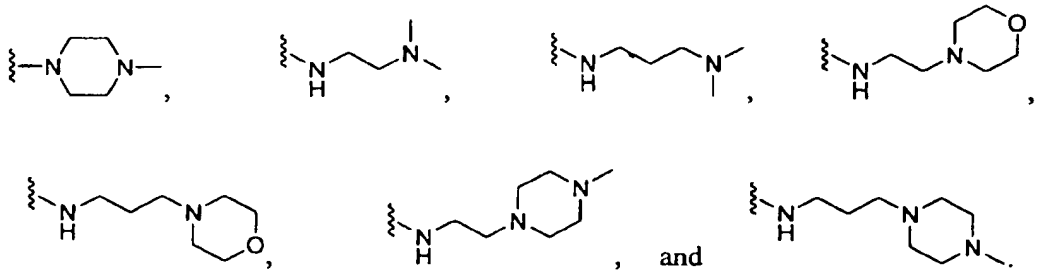


207. A compound as in claim 201, wherein R_8 is Y_3.

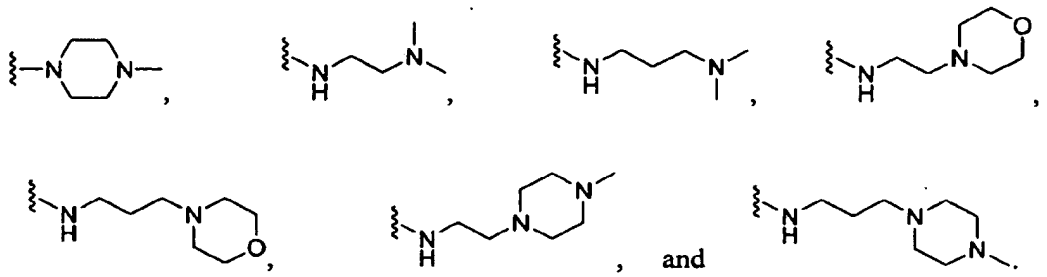
208. A compound as in claim 207, wherein R_3, R_6, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

209. A compound as in claim 207, wherein R_3, R_6, and R_7 are hydrogen.

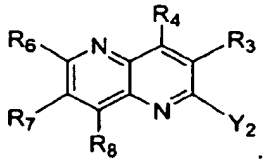
210. A compound as in claim 209, wherein R_4 is selected from



211. A compound as in claim 210, wherein Y_2 is selected from



212. A compound as in claim 178, having the structure



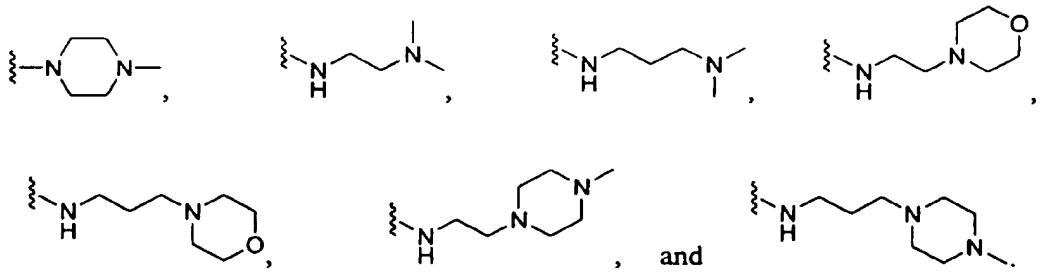
(XVII)

213. A compound as in claim 212, wherein R_6 is Y_3.

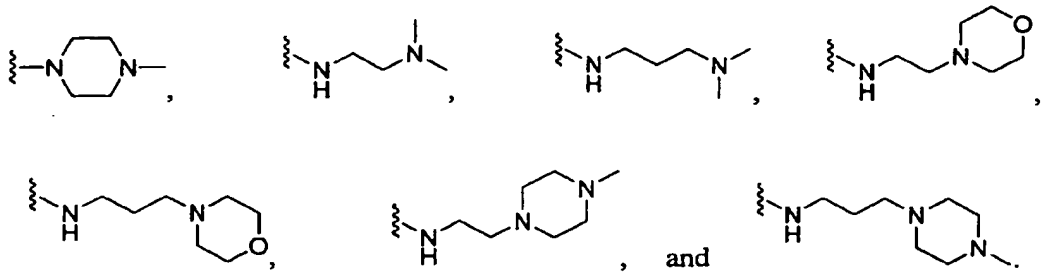
214. A compound as in claim 213, wherein R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

215. A compound as in claim 213, wherein R_3, R_7, and R_8 are hydrogen.

216. A compound as in claim 215, wherein R_4 is selected from



217. A compound as in claim 216, wherein Y_2 is selected from

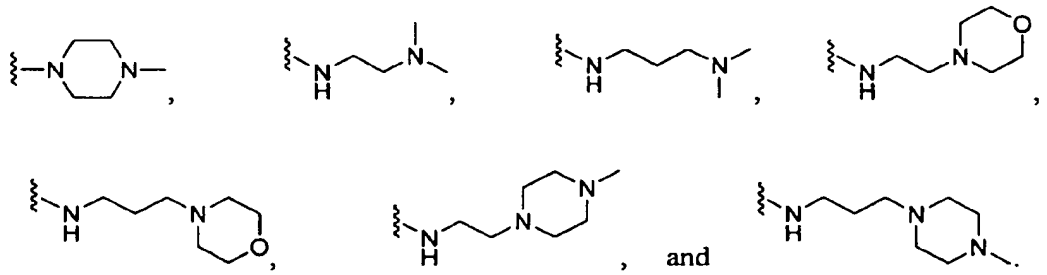


218. A compound as in claim 212, wherein R_8 is Y_3.

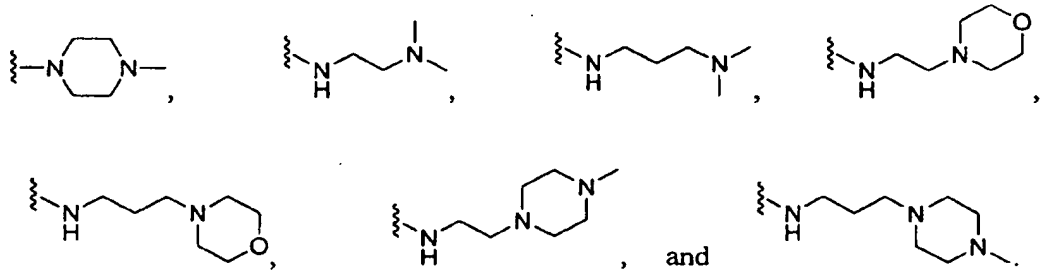
219. A compound as in claim 218, wherein R_3, R_6, and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

220. A compound as in claim 218, wherein R_3, R_6, and R_7 are hydrogen.

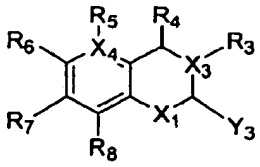
221. A compound as in claim 220, wherein R_4 is selected from



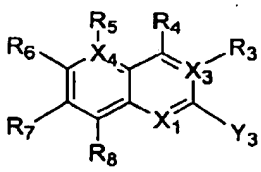
222. A compound as in claim 221, wherein Y_2 is selected from



223. A compound having a structure selected from



and



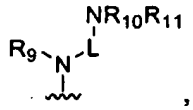
(XVIII) (XIX)

wherein

X_1, X_3, and X_4 are independently nitrogen or carbon;

R_3 is absent, hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide;

R_4 is a group having the structure,



where R_9 is hydrogen or optionally substituted alkyl; L is optionally substituted alkyl; R_{10} and R_{11} are independently hydrogen or optionally substituted alkyl; and together R_{10} and R_{11} can be joined to form an optionally substituted heterocycle, or together R_9 and one of R_{10} or R_{11} can be joined to form an optionally substituted heterocycle;

R_5 is absent or hydrogen;

R_6 and R_7 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, halide, or Y_2;

R_8 is hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide; and

Y_3 is optionally substituted phenyl;

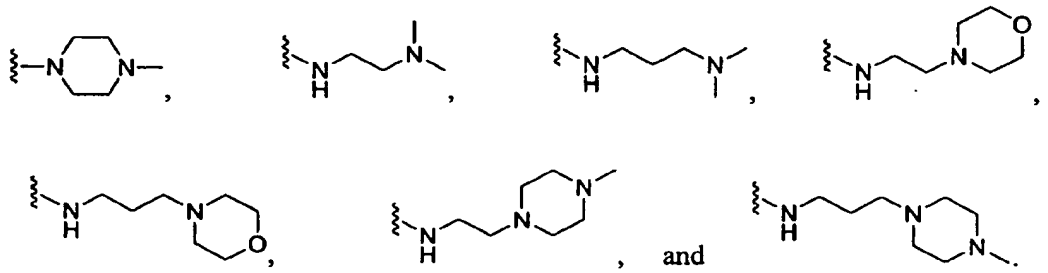
wherein

Y_2 is W-$L_1NR_{12}R_{13}$, where W is O, S, or NR_{14}; L_1 is optionally substituted alkyl; R_{12}, R_{13}, and R_{14} are independently hydrogen or optionally substituted alkyl; and together R_{12} and R_{13} can be joined to form an optionally substituted heterocycle, or together R_{14} and one of R_{12} or R_{13} can be joined to form an optionally substituted heterocycle.

224. A compound as in claim 223, wherein at least one of X_1, X_3, and X_4 is nitrogen.

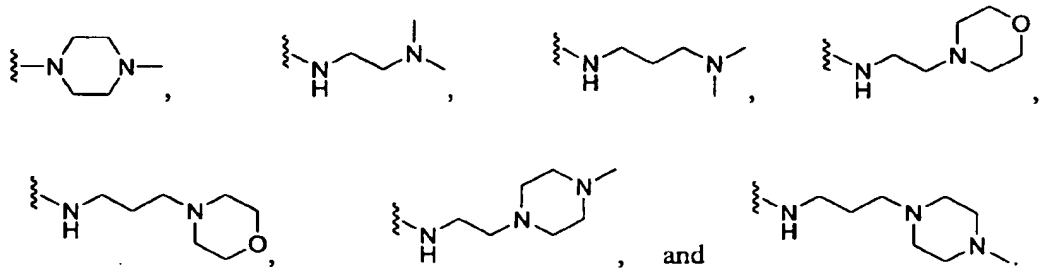
225. A compound as in claim 223, wherein at least two of X_1, X_3, and X_4 are nitrogen.

226. A compound as in claim 223, wherein R_4 is selected from



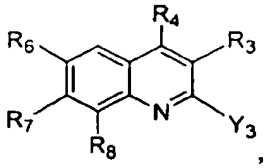
and

227. A compound as in claim 223, wherein Y_2 is selected from

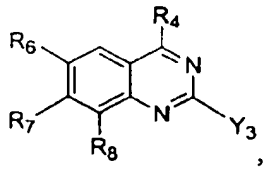


and

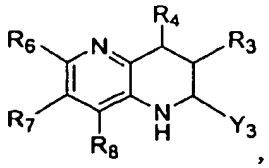
228. A compound as in claim 223, having a structure selected from



(XX)

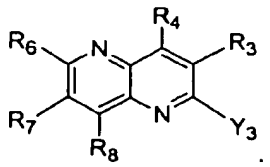


(XXI)



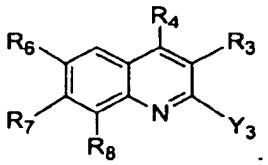
(XXII)

and



(XXIII)

229. A compound as in claim 228, having the structure



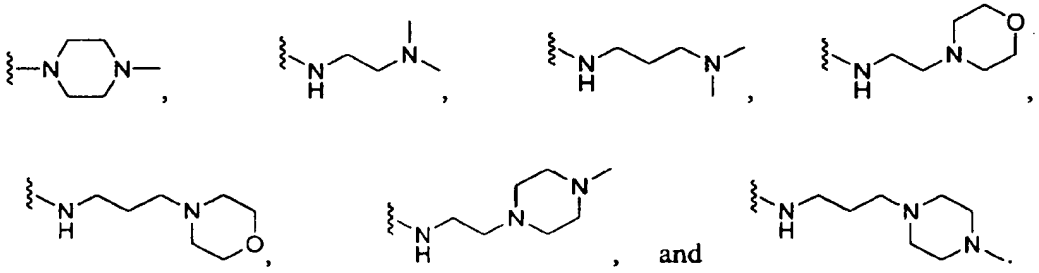
(XX)

230. A compound as in claim 229, wherein R_6 is Y_2.

231. A compound as in claim 230, wherein R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

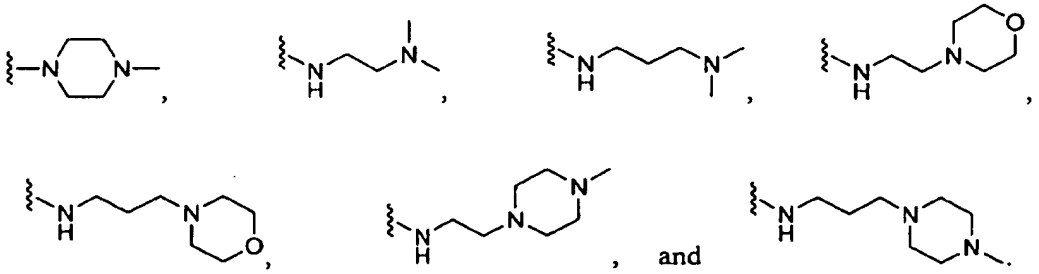
232. A compound as in claim 230, wherein R_3, R_7, and R_8 are hydrogen.

233. A compound as in claim 232, wherein R_4 is selected from



and

234. A compound as in claim 233, wherein Y_2 is selected from



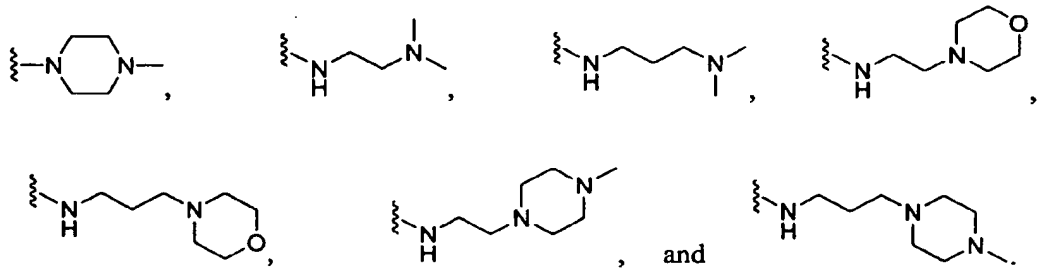
and

235. A compound as in claim 229, wherein R_7 is Y_2.

236. A compound as in claim 235, wherein R_3, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

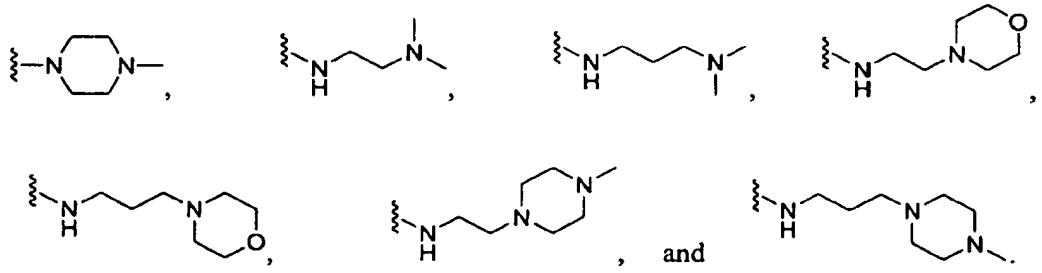
237. A compound as in claim 235, wherein R_3, R_6, and R_8 are hydrogen.

238. A compound as in claim 237, wherein R_4 is selected from



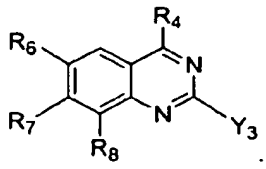
and

239. A compound as in claim 238, wherein Y_2 is selected from



and

240. A compound as in claim 228, having the structure



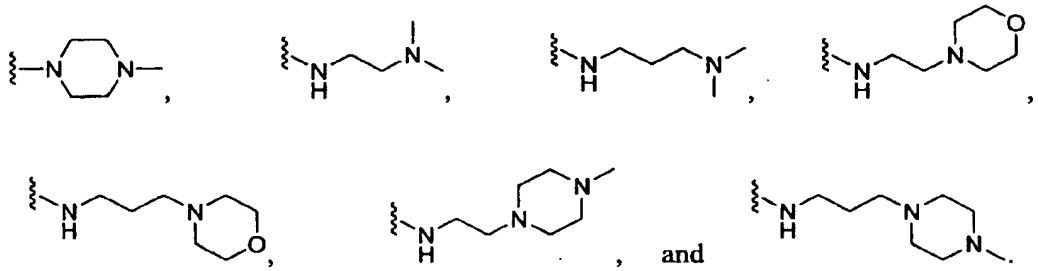
(XXI)

241. A compound as in claim 240, wherein R_6 is Y_2.

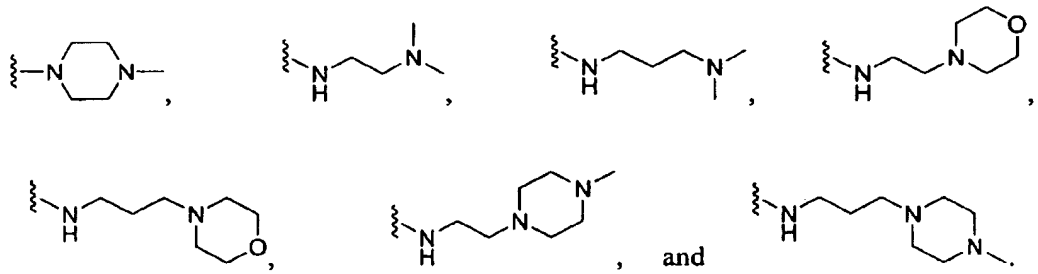
242. A compound as in claim 241, wherein R_7 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

243. A compound as in claim 241, wherein R_7 and R_8 are hydrogen.

244. A compound as in claim 243, wherein R_4 is selected from


and

245. A compound as in claim 244, wherein Y_2 is selected from

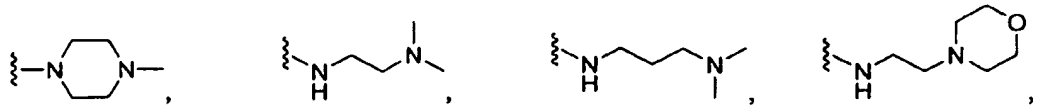

and

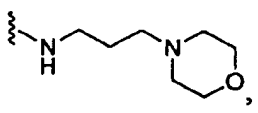
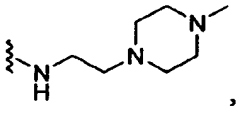
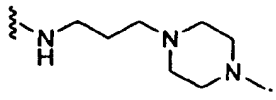
246. A compound as in claim 240, wherein R_7 isY_2.

247. A compound as in claim 246, wherein R_6 and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

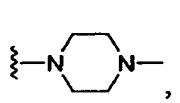
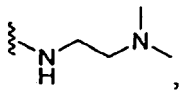
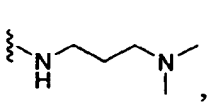
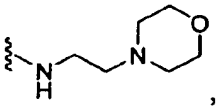
248. A compound as in claim 246, wherein R_6 and R_8 are hydrogen.

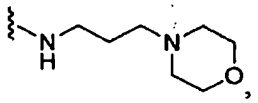
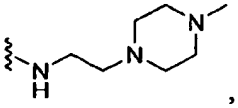
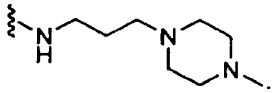
249. A compound as in claim 248, wherein R_4 is selected from



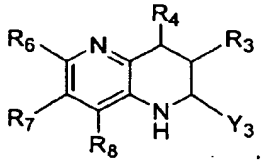
 ,  , and  .

250. A compound as in claim 249, wherein Y_2 is selected from

 ,  ,  ,  ,

 ,  , and  .

251. A compound as in claim 228, having the structure



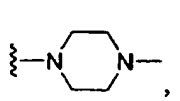
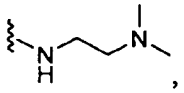
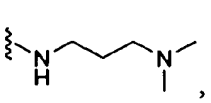
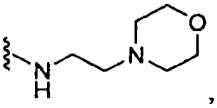
(XXII)

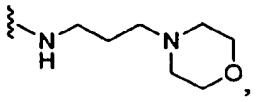
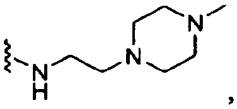
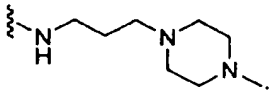
252. A compound as in claim 251, wherein R_6 is Y_2.

253. A compound as in claim 252, wherein R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

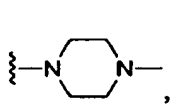
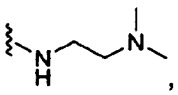
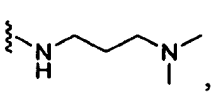
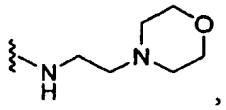
254. A compound as in claim 252, wherein R_3, R_7, and R_8 are hydrogen.

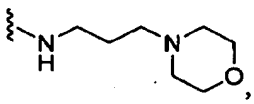
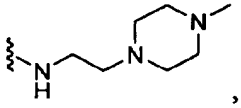
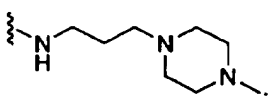
255. A compound as in claim 254, wherein R_4 is selected from

 ,  ,  ,  ,

 ,  , and  .

256. A compound as in claim 255, wherein Y_2 is selected from

 ,  ,  ,  ,

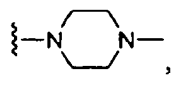
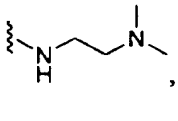
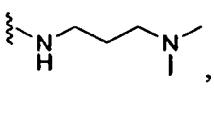
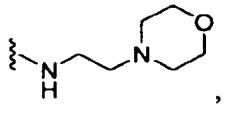
 ,  , and  .

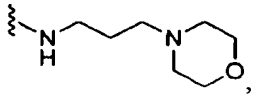
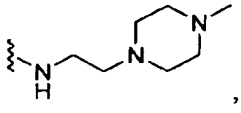
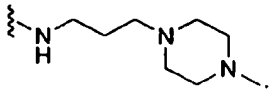
257. A compound as in claim 251, wherein R_7 is Y_2.

258. A compound as in claim 257, wherein R_3, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

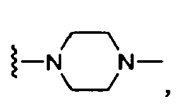
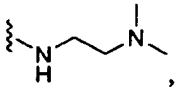
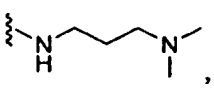
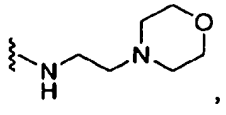
259. A compound as in claim 257, wherein R_3, R_6, and R_8 are hydrogen.

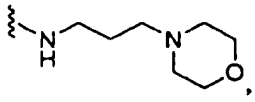
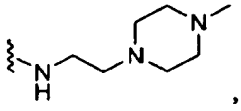
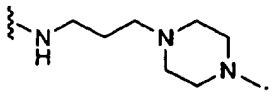
260. A compound as in claim 259, wherein R_4 is selected from

 ,  ,  ,  ,

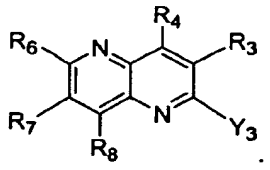
 ,  , and  .

261. A compound as in claim 260, wherein Y_2 is selected from

 ,  ,  ,  ,

 ,  , and  .

262. A compound as in claim 228, having the structure



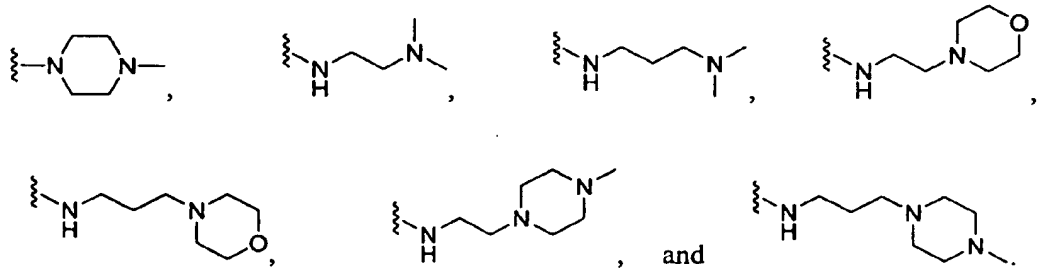
(XXIII)

263. A compound as in claim 262, wherein R_6 is Y_2.

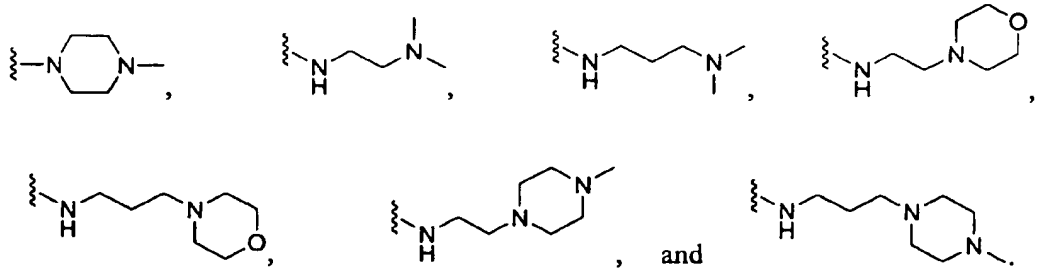
264. A compound as in claim 263, wherein R_3, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

265. A compound as in claim 263, wherein R_3, R_7, and R_8 are hydrogen.

266. A compound as in claim 265, wherein R_4 is selected from



267. A compound as in claim 266, wherein Y_2 is selected from

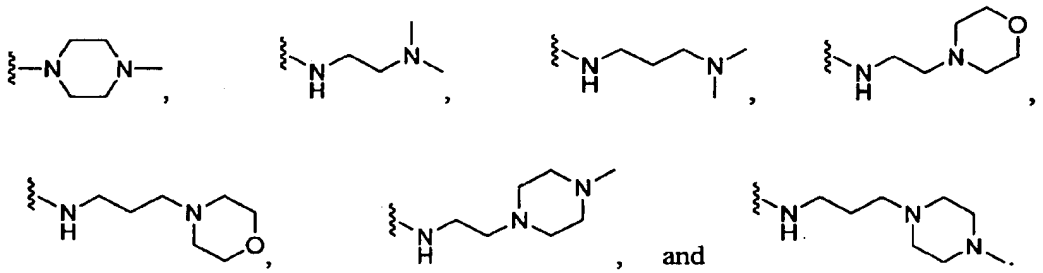


268. A compound as in claim 262, wherein R_7 is Y_2.

269. A compound as in claim 268, wherein R_3, R_6, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

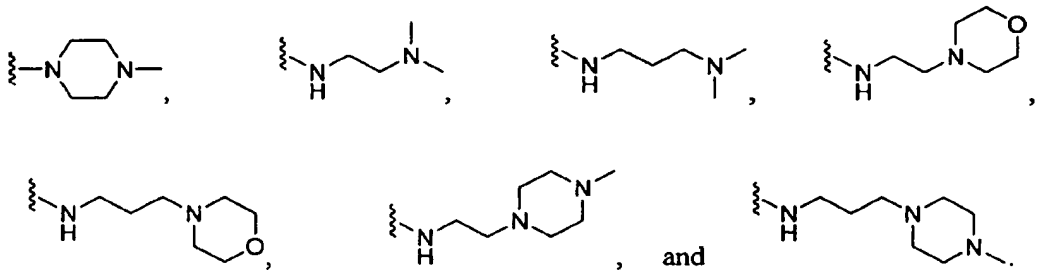
270. A compound as in claim 268, wherein R_3, R_6, and R_8 are hydrogen.

271. A compound as in claim 270, wherein R_4 is selected from



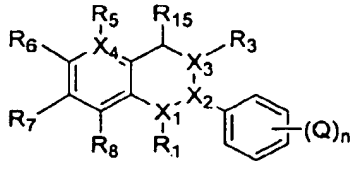
and

272. A compound as in claim 271, wherein Y_2 is selected from



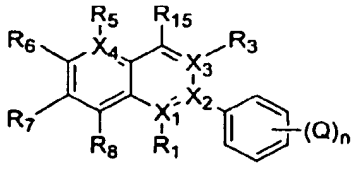
and

273. A compound having a structure selected from



(XXIV)

and



(XXV)

wherein

X_1, X_2, X_3, and X_4 are independently nitrogen or carbon;

R_1, R_3, and R_5 are independently absent, hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide;

R_6 is independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, halide, or Y_2;

R_7, R_8, and R_{15} are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide;

each Q is independently optionally substituted alkyl or Y_2; and

n is an integer from 1-5;

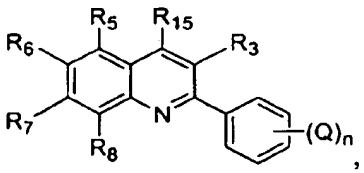
wherein

Y_2 is W-$L_1NR_{12}R_{13}$, where W is O, S, or NR_{14}; L_1 is optionally substituted alkyl; R_{12}, R_{13}, and R_{14} are independently hydrogen or optionally substituted alkyl; and together R_{12} and R_{13} can be joined to form an optionally substituted heterocycle, or together R_{14} and one of R_{12} or R_{13} can be joined to form an optionally substituted heterocycle.

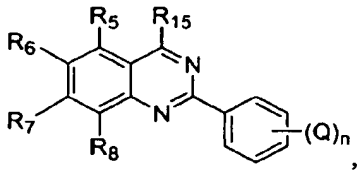
274. A compound as in claim 273, wherein at least one of X_1, X_2, X_3, and X_4 is nitrogen.

275. A compound as in claim 273, wherein at least two of X_1, X_2, X_3, and X_4 are nitrogen.

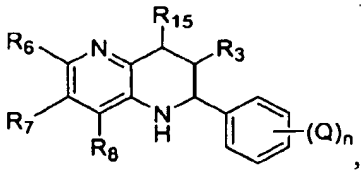
276. A compound as in claim 273, having a structure selected from



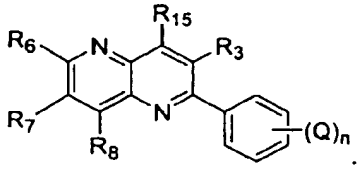
(XXVI),



(XXVII),

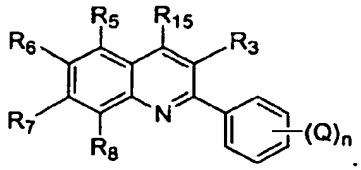


(XXVIII), and



(XXIX).

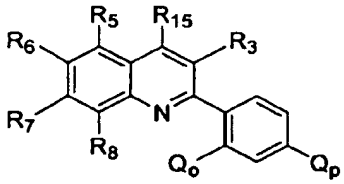
277. A compound as in claim 276, having the structure



(XXVI)

278. A compound as in claim 277, wherein each and every Q is Y_2.

279. A compound as in claim 277, having the structure



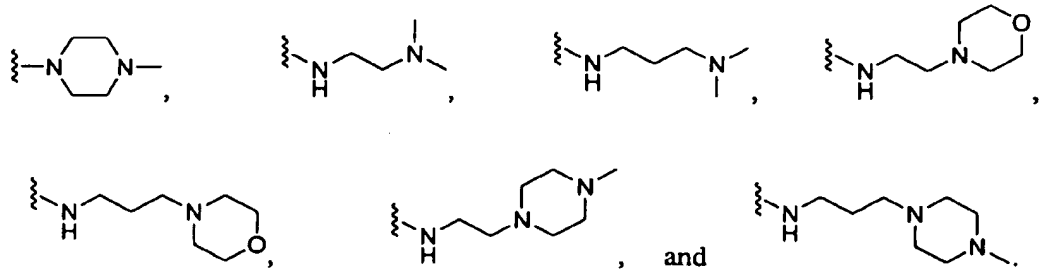
(XXX)

280. A compound as in claim 279, wherein Q_p and Q_o are independently Y_2.

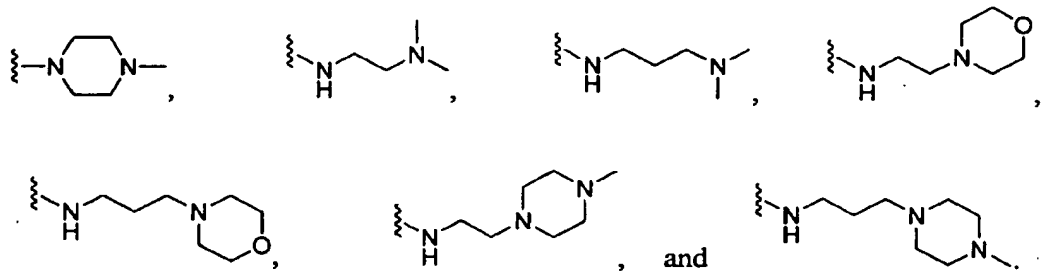
281. A compound as in claim 280, wherein R_3, R_{15}, R_5, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

282. A compound as in claim 280, wherein R_3, R_{15}, R_5, R_6, R_7, and R_8 are hydrogen.

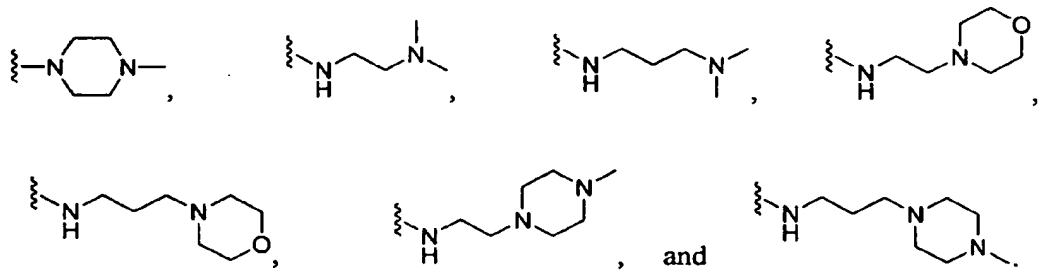
283. A compound as in claim 282, wherein Q_p is selected from



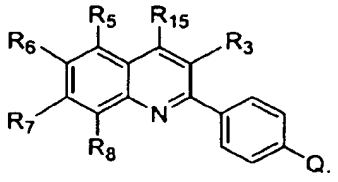
284. A compound as in claim 282, wherein Q_o is selected from



285. A compound as in claim 282, wherein Q_p and Q_o are independently selected from



286. A compound as in claim 277, having the structure



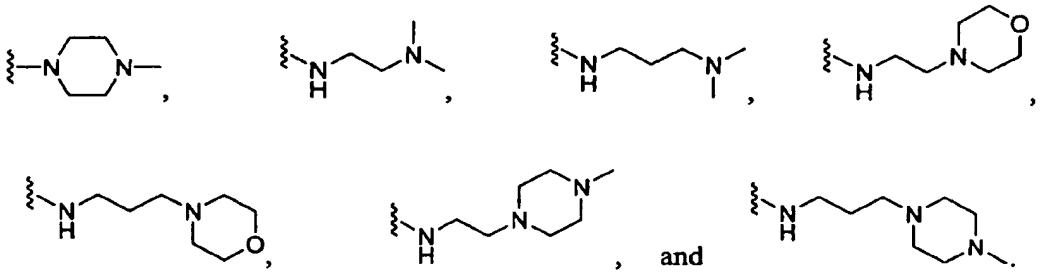
(XXXI)

287. A compound as in claim 286, wherein R_6 is Y_2.

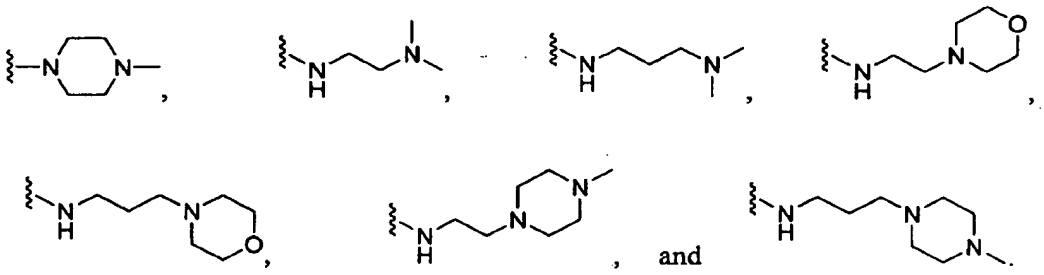
288. A compound as in claim 287, wherein Q is Y_2.

289. A compound as in claim 288, wherein R_3, R_{15}, R_5, R_7, and R_8 are hydrogen.

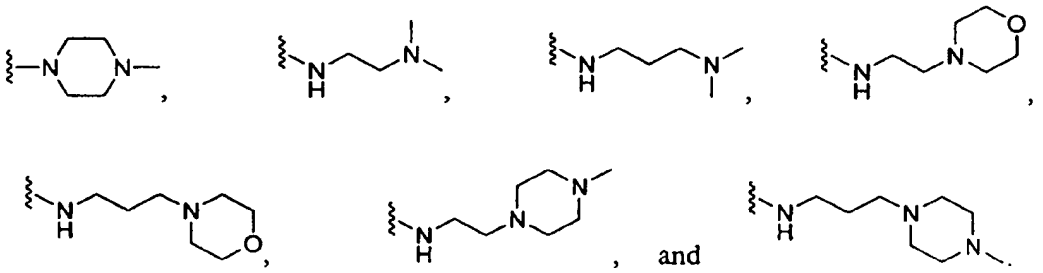
290. A compound as in claim 289, wherein R_6 is selected from



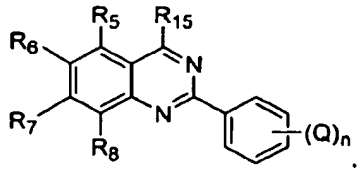
291. A compound as in claim 289, wherein Q is selected from



292. A compound as in claim 289, wherein R_6 and Q are independently selected from



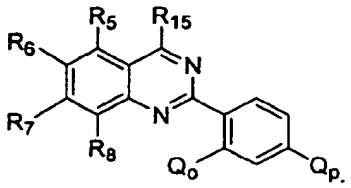
293. A compound as in claim 276, having the structure



(XXVII)

294. A compound as in claim 293, wherein each and every Q is Y_2.

295. A compound as in claim 293, having the structure



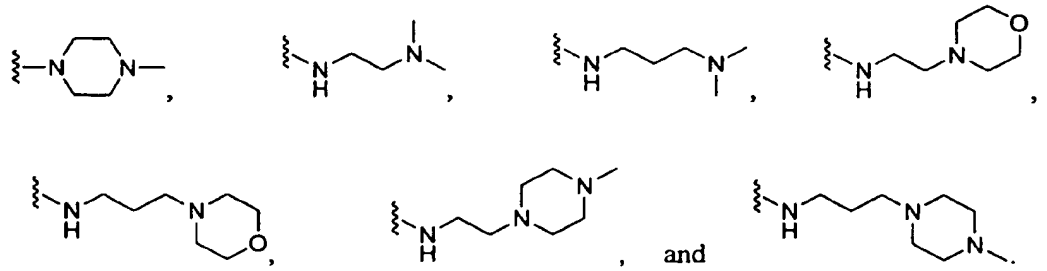
(XXXII)

296. A compound as in claim 295, wherein Q_p and Q_o are independently Y_2.

297. A compound as in claim 296, wherein R_{15}, R_5, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

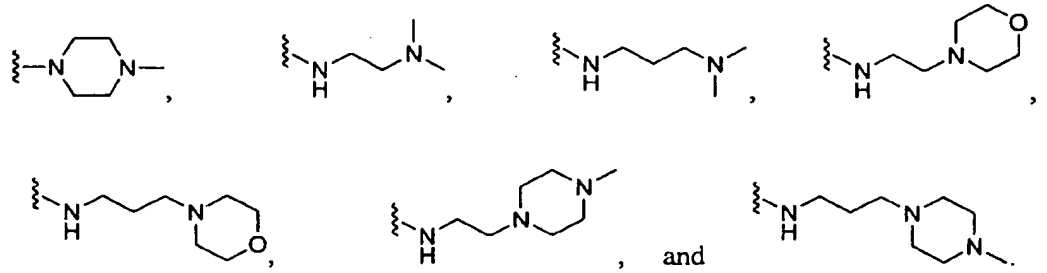
298. A compound as in claim 296, wherein R_{15}, R_5, R_6, R_7, and R_8 are hydrogen.

299. A compound as in claim 298, wherein Q_p is selected from



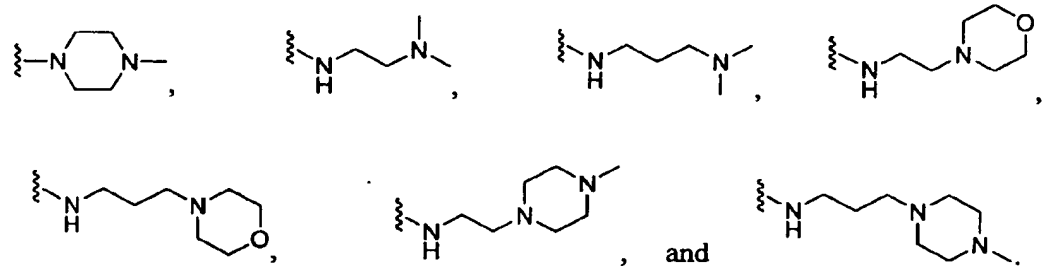
and

300. A compound as in claim 298, wherein Q_o is selected from

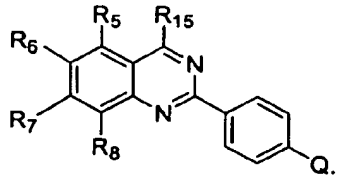


and

301. A compound as in claim 298, wherein Q_p and Q_o are independently selected from



302. A compound as in claim 293, having the structure



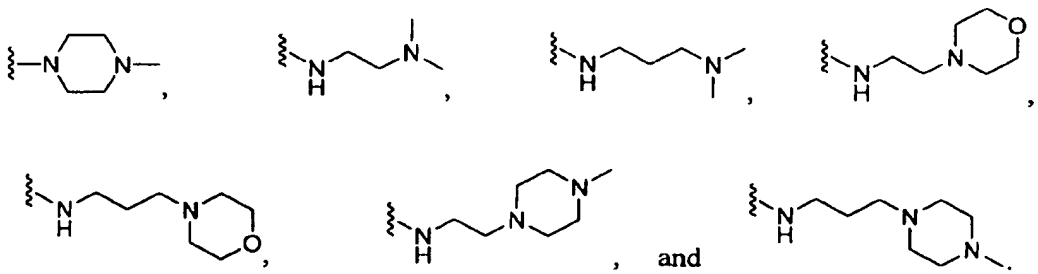
(XXXIII)

303. A compound as in claim 302, wherein R_6 is Y_2.

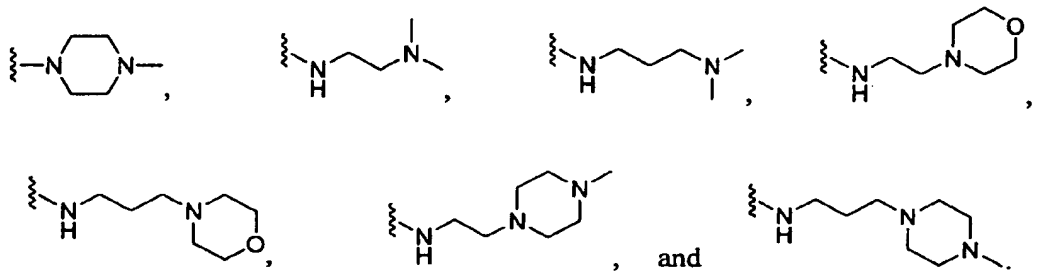
304. A compound as in claim 303, wherein Q is Y_2.

305. A compound as in claim 304, wherein R_{15}, R_5, R_7, and R_8 are hydrogen.

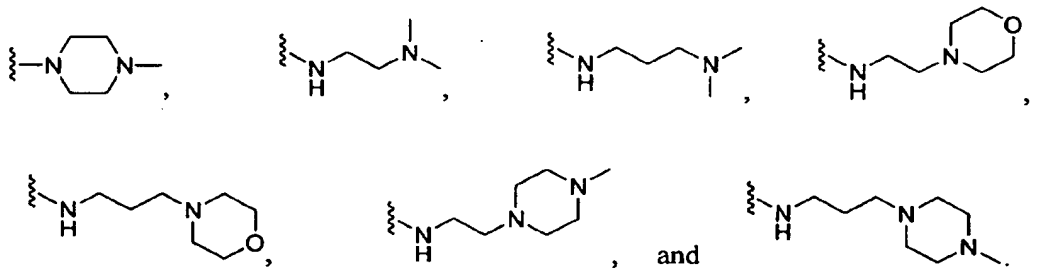
306. A compound as in claim 305, wherein R_6 is selected from



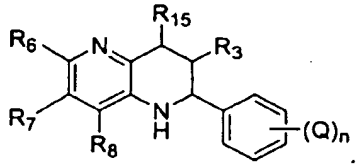
307. A compound as in claim 305, wherein Q is selected from



308. A compound as in claim 305, wherein R_6 and Q are independently selected from



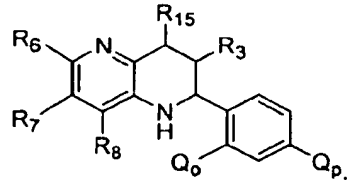
309. A compound as in claim 276, having the structure



(XXVIII)

310. A compound as in claim 309, wherein each and every Q is Y_2.

311. A compound as in claim 309, having the structure



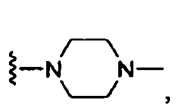
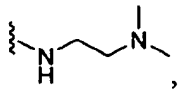
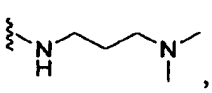
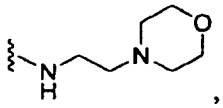
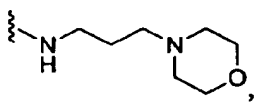
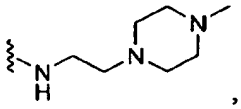
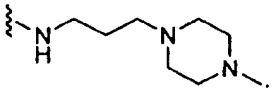
(XXXIV)

312. A compound as in claim 311, wherein Q_p and Q_o are independently Y_2.

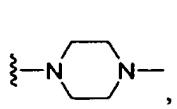
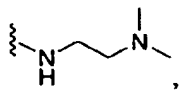
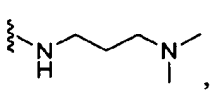
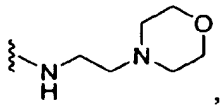
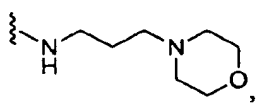
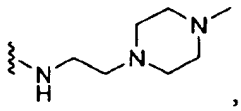
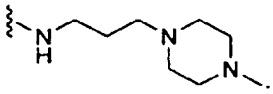
313. A compound as in claim 312, wherein R_3, R_{15}, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

314. A compound as in claim 312, wherein R_3, R_{15}, R_6, R_7, and R_8 are hydrogen.

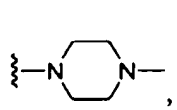
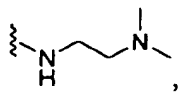
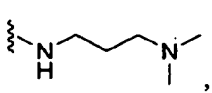
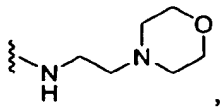
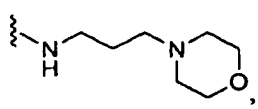
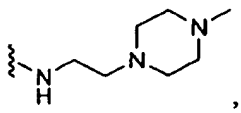
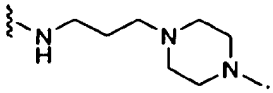
315. A compound as in claim 314, wherein Q_p is selected from







and


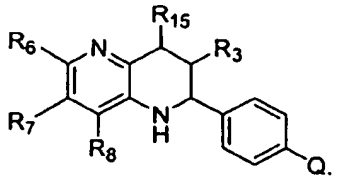
316. A compound as in claim 314, wherein Q_o is selected from







and


317. A compound as in claim 314, wherein Q_p and Q_o are independently selected from







and


318. A compound as in claim 309, having the structure



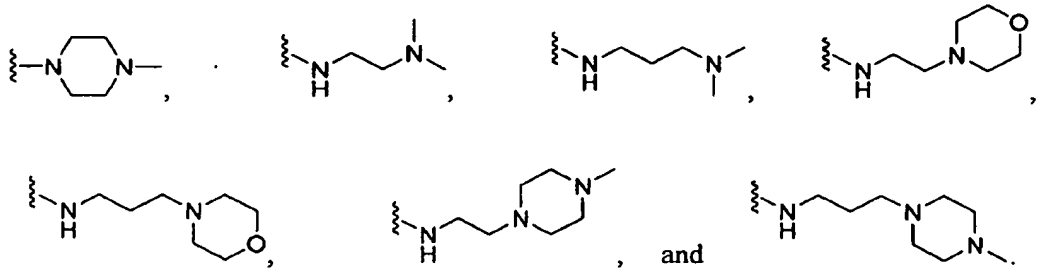
(XXXV)

319. A compound as in claim 318, wherein R_6 is Y_2.

320. A compound as in claim 319, wherein Q is Y_2.

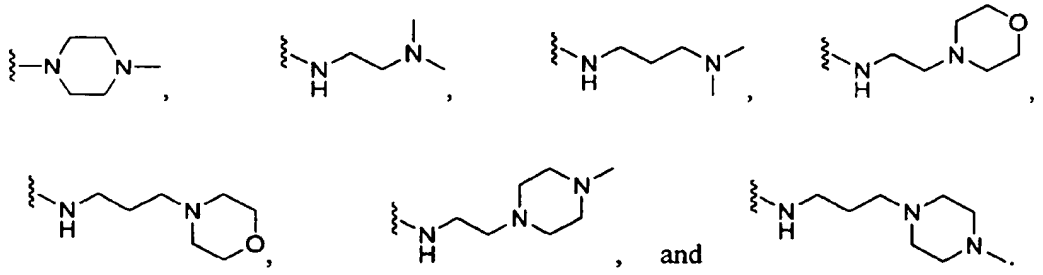
321. A compound as in claim 320, wherein R_3, R_{15}, R_7, and R_8 are hydrogen.

322. A compound as in claim 321, wherein R_6 is selected from



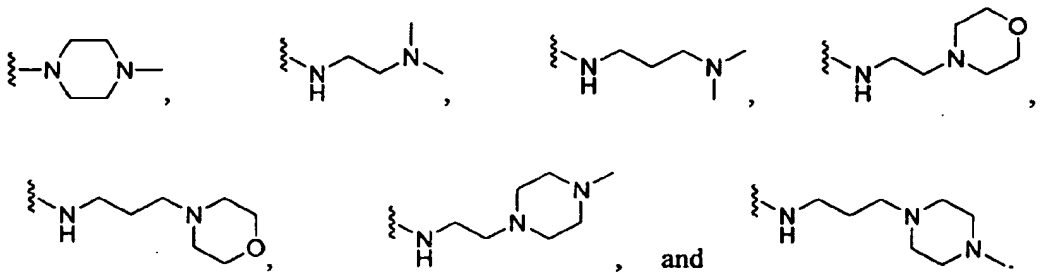
and

323. A compound as in claim 321, wherein Q is selected from

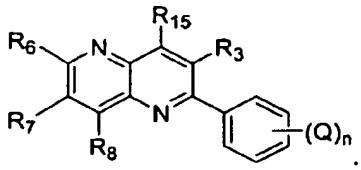


and

324. A compound as in claim 321, wherein R_6 and Q are independently selected from



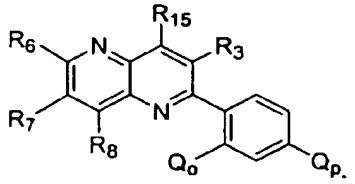
325. A compound as in claim 276, having the structure



(XXIX)

326. A compound as in claim 325, wherein each and every Q is Y_2.

327. A compound as in claim 325, having the structure



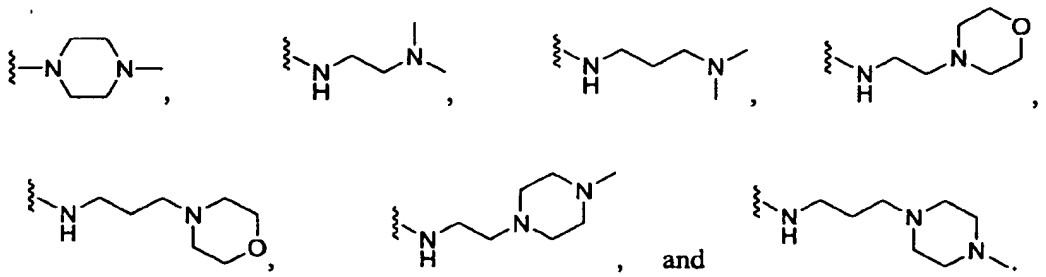
(XXXVI)

328. A compound as in claim 327, wherein Q_p and Q_o are independently Y_2.

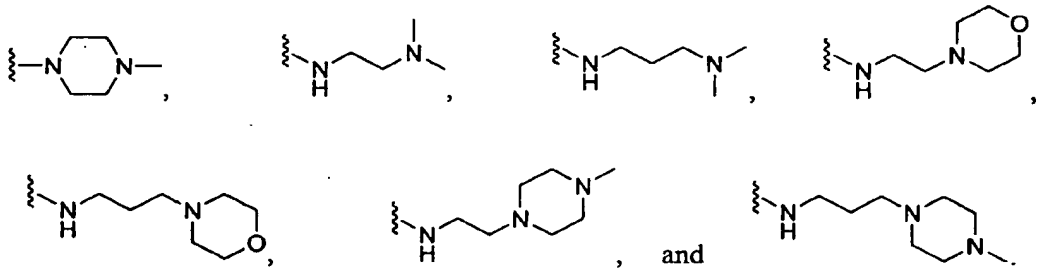
329. A compound as in claim 328, wherein R_3, R_{15}, R_6, R_7, and R_8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, or halide.

330. A compound as in claim 328, wherein R_3, R_{15}, R_5, R_6, R_7, and R_8 are hydrogen.

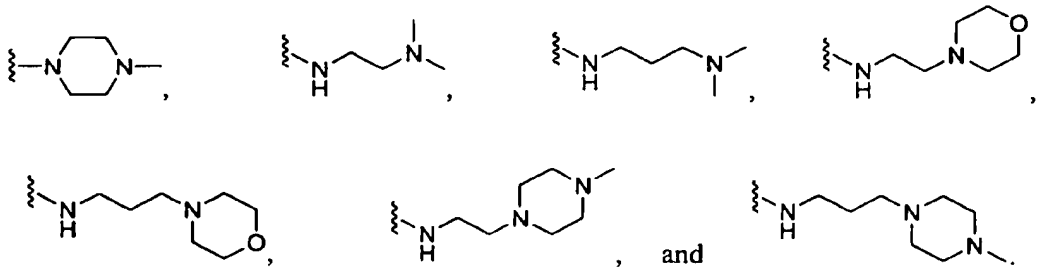
331. A compound as in claim 330, wherein Q_p is selected from



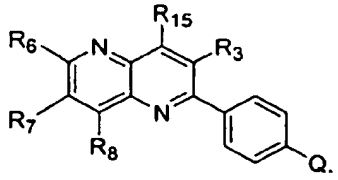
332. A compound as in claim 330, wherein Q_o is selected from



333. A compound as in claim 330, wherein Q_p and Q_o are independently selected from



334. A compound as in claim 309, having the structure



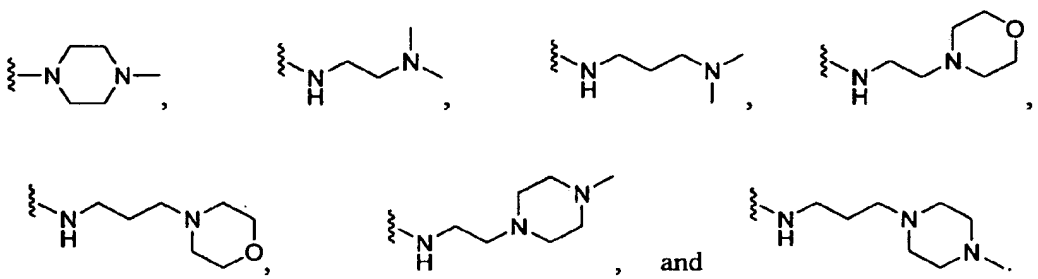
(XXXVII)

335. A compound as in claim 334, wherein R_6 is Y_2.

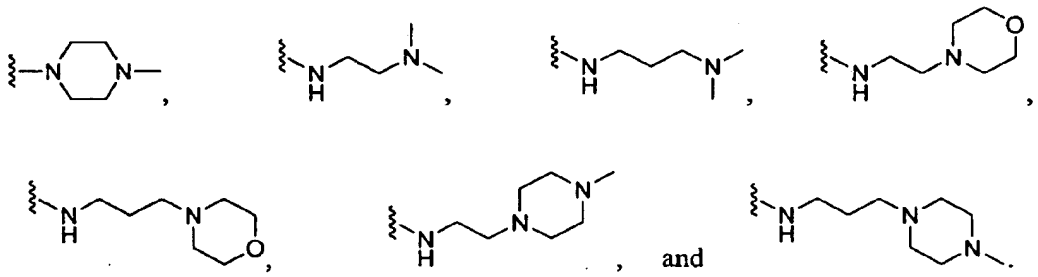
336. A compound as in claim 335, wherein Q is Y_2.

337. A compound as in claim 336, wherein R_3, R_{15}, R_7, and R_8 are hydrogen.

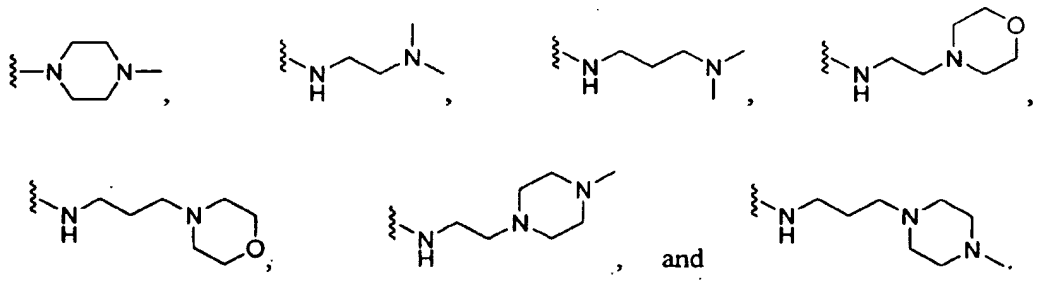
338. A compound as in claim 337, wherein R_6 is selected from


and

339. A compound as in claim 337, wherein Q is selected from


and

340. A compound as in claim 337, wherein R_6 and Q are independently selected from


and

341. A pharmaceutical composition, comprising a compound of any one of claims 1-156 and a pharmaceutically acceptable carrier.

342. The pharmaceutical composition of claim 341, wherein the pharmaceutical composition is formulated for oral administration.

343. The pharmaceutical composition of claim 341, wherein the pharmaceutical composition is formulated for parenteral administration.

344. A pharmaceutical composition, comprising a compound of any one of claims 157-172 and a pharmaceutically acceptable carrier.

345. The pharmaceutical composition of claim 344, wherein the pharmaceutical composition is formulated for oral administration.

346. The pharmaceutical composition of claim 344, wherein the pharmaceutical composition is formulated for parenteral administration.

347. A pharmaceutical composition, comprising a compound of any one of claims 173-222 and a pharmaceutically acceptable carrier.

348. The pharmaceutical composition of claim 347, wherein the pharmaceutical composition is formulated for oral administration.

349. The pharmaceutical composition of claim 347, wherein the pharmaceutical composition is formulated for parenteral administration.

350. A pharmaceutical composition, comprising a compound of any one of claims 223-272 and a pharmaceutically acceptable carrier.

351. The pharmaceutical composition of claim 350, wherein the pharmaceutical composition is formulated for oral administration.

352. The pharmaceutical composition of claim 350, wherein the pharmaceutical composition is formulated for parenteral administration.

353. A pharmaceutical composition, comprising a compound of any one of claims 273-340 and a pharmaceutically acceptable carrier.

354. The pharmaceutical composition of claim 353, wherein the pharmaceutical composition is formulated for oral administration.

355. The pharmaceutical composition of claim 353, wherein the pharmaceutical composition is formulated for parenteral administration.

356. A method for reducing signaling by a Toll-like receptor (TLR), comprising contacting a cell expressing a TLR, selected from TLR7, TLR8, and TLR9, with an effective amount of a compound according to any one of claims 1-340 to reduce signaling by the TLR in response to an agonist of the TLR, compared to signaling by the TLR in response to the agonist in absence of the contacting.

357. The method of claim 356, wherein the TLR is TLR7.

358. The method of claim 356, wherein the TLR is TLR8.

359. The method of claim 356, wherein the TLR is TLR9.

360. The method of claim 356, wherein the agonist of the TLR is a CpG nucleic acid.

361. The method of claim 356, wherein the agonist of the TLR is RNA.

362. The method of claim 356, wherein the contacting occurs *in vitro*.

363. The method of claim 356, wherein the cell expressing the TLR is an immune cell.

364. The method of claim 356, wherein the cell expressing the TLR is a cell that is modified to express the TLR.

365. A method for reducing an immune response, comprising

contacting a population of immune cells expressing a Toll-like receptor (TLR), selected from TLR7, TLR8, and TLR9, with an effective amount of a compound according to any one of claims 1-340 to reduce an immune response by the immune cells, compared to an immune response by the immune cells in absence of the contacting.

366. The method of claim 365, wherein the TLR is TLR7.

367. The method of claim 365, wherein the TLR is TLR8.

368. The method of claim 365, wherein the TLR is TLR9.

369. The method of claim 365, wherein the contacting occurs *in vitro*.

370. The method of claim 365, wherein the contacting occurs *in vivo*.

371. The method of claim 365, wherein the immune response is a Th1-like immune response.

372. The method of claim 365, wherein the immune response is secretion of a cytokine.

373. The method of claim 365, wherein the immune response is secretion of a chemokine.

374. The method of claim 365, wherein the immune response is an immune response to an antigen.

375. The method of claim 374, wherein the antigen is an allergen.

376. The method of claim 374, wherein the antigen is a microbial antigen.

377. The method of claim 374, wherein the antigen is an antigen characteristic of an autoimmune condition.

378. A method for treating an autoimmune condition in a subject, comprising administering to a subject having an autoimmune condition, wherein the autoimmune condition involves signaling by a Toll-like receptor (TLR) selected from TLR7, TLR8, and TLR9, an effective amount of a compound according to any one of claims 1-340 to treat the autoimmune condition.

379. The method of claim 378, wherein the TLR is TLR7.

380. The method of claim 378, wherein the TLR is TLR8.

381. The method of claim 378, wherein the TLR is TLR9.

382. The method of claim 378, wherein the autoimmune condition is selected from ankylosing spondylitis, atherosclerosis, autoimmune chronic active hepatitis, autoimmune encephalomyelitis, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, autoimmune-associated infertility, Behçet's syndrome, bullous pemphigoid, Churg-Strauss disease, Crohn's disease, glomerulonephritis, Goodpasture's syndrome, Grave's disease, Guillain-Barré syndrome, Hashimoto's thyroiditis, idiopathic Addison's disease, insulin-dependent diabetes mellitus, insulin resistance, mixed connective tissue disease, multiple sclerosis, myasthenia gravis, pemphigus, pernicious anemia, polyarteritis nodosa, polymyositis, primary biliary sclerosis, psoriasis, rheumatoid arthritis, sarcoidosis, scleroderma, sclerosing cholangitis, Sjögren's syndrome, systemic lupus erythematosus, Takayasu's arteritis, temporal arteritis, ulcerative colitis, and Wegener's granulomatosis.

383. The method of claim 378, wherein the autoimmune condition is systemic lupus erythematosus.

384. The method of claim 378, wherein the autoimmune condition is rheumatoid arthritis.

385. The method of claim 378, wherein the subject is a human.